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(54) Title: TREATMENT OF IMMUNE DISEASES

(57) Abstract

The present invention provides a method, compounds, and compositions for treating a disease associated with immune dysfunction. In accordance with the method, a pharmacologically-acceptable composition including at least one compound selected from the group of compounds consisting of 5-alkyl-resorcinol derivatives, cannabinol derivatives, cannabidiol derivatives, cannabigerol derivatives, and combinations thereof is administered to a patient under conditions sufficient to attenuate the dysfunction within the immune system. The invention also provides an antiviral cannabinol derivative that can be used in the inventive method. The invention also provides an alkylated resorcinol derivative and a method of using the alkylated resorcinol derivative to attenuate the growth of a neoplasm. The method and compound are useful for treating diseases of the immune system, such as HIV disease and neoplastic disorders.

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TREATMENT OF IMMUNE DISEASES

TECHNICAL FIELD OF THE INVENTION

The present invention pertains to a treatment for diseases associated with
5 immune dysfunction, particularly HIV disease and neoplastic disorders.

BACKGROUND OF THE INVENTION

The retroviral Human Immunodeficiency Viruses 1 and 2 (HIV) are the most common causative agents of AIDS. Through a portion of a viral envelope protein 10 (gp120), HIV binds specifically and with high affinity to the CD4 molecule on T-lymphocytes. Following binding, the virus fuses with the cell membrane and is internalized. Within the cell, it produces a reverse transcriptase which transcribes its genomic RNA to DNA. The reverse HIV transcript is then integrated into the cellular DNA where it exists for the life of the cell as a "provirus." The provirus can remain 15 latent for an indefinite period of time, or it can be "activated" to transcribe mRNA and genomic RNA, leading to protein synthesis, assembly, new virion formation, budding of virus from the cell surface, and cell death.

While the precise events triggering activation are poorly understood, they appear to lead to liberation/production of endogenous cellular factors that interact with the HIV 20 genome to promote translation. In this regard, binding of cellular SP1 to the HIV promoter (which contains several tandem SP1 consensus binding sites) is needed for high-level transcription of the latent HIV genome. Additionally, NF κ B functions as a potent transcriptional activator when it binds to one or two (depending on the HIV strain) consensus binding sites in the HIV enhancer, which is adjacent to the promoter. 25 The transcription factors CREB/ATF, NF-AT, and AP1 also potentiate HIV transcription. As for all retroviruses, the structural and enzymatic gag, pol and env gene products are produced when the provirus is activated. HIV first transcribes gag-pol as a fusion protein which is ultimately cleaved by the HIV protease enzyme to yield the mature viral proteins. HIV also employs additional regulatory proteins (specifically the 30 tat and rev gene products) as transcriptional enhancers to induce high levels of gene expression. Nef is another HIV gene that modulates viral replication levels.

While the set of factors triggering active viral replication remains only partially understood, some of them include heat shock, ultraviolet radiation, regulatory proteins of other (e.g., superinfecting) viruses, inflammatory cytokines (e.g., IL1, IL2, IL4, IL6, 35 IL10, Tumor Necrosis Factor α (TNF α), Platelet Activating Factor, Interferon γ (IFN γ)), and Nitric Oxide. Many of these factors are T-cell activators (e.g., they precipitate cell cycling and clonal expansion of T-cell populations), and they are released by many B-cells in direct response to infectious agents (such as HIV). Such factors also trigger

intracellular signaling events promoting the production of NF κ B and its dissociation from its inhibitor (I κ B). Active NF κ B is a DNA binding protein activating the transcription of many cellular genes, and also the HIV genome. In this regard, cytokines such as TNF α and IL-1 augment NF κ B activity in cultured T-cells.

5 Some cells harboring the provirus express HIV gp41, gp120, and possibly other viral proteins, presumably through basal levels of transcription from the proviral genome. While a host immune response is mounted against such HIV proteins, due in part to the high degree of mutability of such proteins and their varied glycosylation patterns, such immune response usually is incomplete, resulting in a pool of latent virus
10 that effectively avoids immune surveillance. Additionally, the presence of HIV gp120 in the membranes of infected cells can mediate fusion events between infected cells and non-infected antigen-presenting cells (e.g., dendritic cells) via a reaction similar to that by which the virus enters uninfected cells. Rather than destroy infected cells, as might be expected for a cellular immune response, such fusion events typically lead to the
15 formation of short-lived multinucleated syncytial "giant cells," which actually facilitate viral replication. In this regard, while latently-infected monocytes and T-lymphocytes normally are quiescent and have no active NF κ B, other cells (e.g., dendritic cells) normally contain high levels of active NF κ B. However, dendritic cells do not produce SP1, while T-cells and monocytes express Sp1 in active form. Formation of syncytia
20 between infected T-cells and dendritic cells, thus, brings active NF κ B and SP1 into the same cell, facilitating transcription of the HIV genome.

The viral life cycle ends when mature HIV are "budded" from the host cell, retaining some amount of cell membrane as part of its envelope. Oftentimes, these budding events are localized to areas of the cell membrane where intracellular adhesion molecules (ICAMs) and other surface receptors coalesce during the cell's activation process. Because such proteins localize to regions of intercellular contact, this phenomenon (known as polar capping or polarization) can help spread the viral infection by "focusing" viral budding to an adjacent cell or in facilitating syncytia formation.
25 Moreover, liberated virions often contain some membrane-bound ICAMs (e.g., ICAM-1), and such viruses can bind cells (e.g., peripheral blood mononuclear cells) through interactions not involving the gp120-CD4 interaction. Such ICAM-1 $^+$ HIV viruses are more infective than ICAM-1 $^-$ HIV, and since they are cloaked with the host animal's glycoproteins, they are much less likely to be neutralized by circulating host antibodies.
30 HIV can augment production of cell adhesion molecules such as ICAM-1 by precipitating the phosphorylation of STAT1 α , which binds to the ICAM-1 gene enhancer and promotes SP1-dependent transcription. Interestingly, inflammatory cytokines (e.g., IFN γ) also precipitate phosphorylation of STAT1 α , and the gene
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contains consensus binding sites for some of the same transcription factors involved in HIV replication, notably NF κ B.

The presence of latent pools of HIV within quiescent cells, the high mutability of HIV proteins and their relative invisibility to immune surveillance, and the ability of the virus to alter its tropism by acquiring ICAMs all permit the virus to replicate in the face of an aggressive host immune response. Over time, the virus gradually subverts and progressively destroys the very system relied on to ward off infections. This progression of viral persistence and replication is HIV disease, and it is marked by dysregulation of cytokine signaling, particularly in the lymphatic system, and ultimate destruction of lymph nodes. When HIV disease has progressed to the point where the host's immune system becomes so incapacitated that it is unable to ward off opportunistic diseases (e.g., bacteria, fungi, neoplasms, etc.), AIDS develops. Many patients begin to develop AIDS symptoms when their CD4+ T-cell count drops to about 200 (most healthy adults have a CD4+ T-cell count of about 1000).

To prevent the development of AIDS, many current therapies focus on halting viral life cycle events, typically by directly targeting viral proteins. For example, gp120 antibodies have been produced in an attempt to block initial cell infection. However, due in part to the ability of the virus to spread by syncytia or direct cell-to-cell contact and its ability to acquire ICAM molecules, such attempts have met with mixed results. Other therapies employ inhibitors of HIV protease to block the formation of mature rep and cap from the rep-cap preprotein. Still other regimens employ combinations of antiviral compounds, aimed at inhibiting or attenuating viral enzymes. It has been estimated, however, that spontaneous mutations arise in HIV genes once in about 10^4 replications (Perelson et al., *Science*, 271, 1582-86 (1996)). Given that the virus typically undergoes about 10^{10} replications each day, resistance to agents acting directly against viral proteins is not uncommon. Moreover, many regimens require a patient to adhere to very a strict dosing schedule involving scores of pills each day. Failure of patients to comply with such regimens adds to the failure rate of antiviral therapy. In light of these problems, there is a need for new methods, compounds, and compositions for attenuating the progression of HIV disease and other immune dysfunctions.

Many thousands of people are diagnosed with cancer and other neoplastic disorders each year, and although advances have been made in cancer therapy, the existing treatments are not successful in many cases. For example, many anticancer drugs administered to patients often have toxic effects on non-cancerous cells in the patient's body. Moreover, many neoplastic cells whose growth can be inhibited by certain drugs sometimes become resistant to those drugs. Of course, responsive tumors represent only a small fraction of the various types of neoplastic disease and, notably, there are relatively few drugs highly active against solid tumors such as ovarian cancer,

breast cancer, lung cancer and the like. Thus, patients with many types of malignancies remain at significant risk for relapse and mortality. As such, there exists a continuing need for agents that inhibit neoplastic growth, especially solid tumor growth.

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BRIEF SUMMARY OF THE INVENTION

The present invention provides a method, compounds, and compositions for treating a disease associated with immune dysfunction. In accordance with the method, a pharmacologically-acceptable composition including at least one 5-alkyl-resorcinol derivative compound selected from the group of compounds consisting of 5-alkyl-
10 resorcinols, cannabinol derivatives, cannabidiol derivatives, cannabigerol derivatives, and combinations thereof is administered to a patient under conditions sufficient to attenuate the dysfunction within the immune system. The invention also provides an antiviral cannabinol derivative that can be used in the inventive method. The invention also provides an alkylated resorcinol derivative and a method of using the alkylated
15 resorcinol derivative to attenuate the growth of a neoplasm. The method and compound are useful for treating diseases of the immune system, such as HIV disease and neoplastic disorders. These and other advantages of the present invention, as well as additional inventive features, will be apparent from the following detailed description.

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DETAILED DESCRIPTION OF THE INVENTION

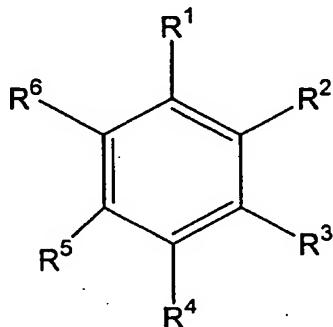
In one aspect, the invention provides a method for treating a disease associated with immune dysfunction. In accordance with the method, a pharmacologically-acceptable composition including at least one compound selected from the group of compounds consisting of 5-alkyl-resorcinol derivatives, cannabinol derivatives,
25 cannabidiol derivatives, cannabigerol derivatives, and combinations thereof is administered to a patient under conditions sufficient to attenuate the dysfunction within the immune system.

The inventive method is particularly effective in combating HIV disease in humans, SIV disease in non-human primates, or FIV in feline animals. Without being bound by any particular theory, it is believed that the inventive method promotes quiescence of both actively- and latently-infected T-cells, monocytes, and macrophages, potentially through a variety of complementing mechanisms. The combination of these effects can attenuate the ability of HIV to replicate in a host immune system. Absent replication, uninfected components of the immune system are better able to clear
30 latently-infected cells from the patient, and fewer mutation events occur. Additionally, by attenuating HIV replication, the method can reduce the probability of interpersonal transmission. (e.g., perinatal or sexual transmission). Indeed, applications of the inventive method in which the composition is administered to mucosal tissue (e.g.,

vaginal or rectal tissue), can retard the uptake of the virus through such tissues, thus reducing the incidence of primary infection. Thus, the invention provides a method of preventing the transmission of HIV. Furthermore, the method can guard against secondary conditions often attending HIV infection, such as destruction of lymphatic structure, CNS disease, opportunistic diseases, neoplasms, and the AIDS Wasting Syndrome.

Treatment of HIV disease can be assessed by monitoring the attenuation of its symptoms in response to the continued application of the inventive method. For example, while most healthy adult humans have a CD4+ T-cell count from between about 800 to about 1200, that of HIV+ patients steadily declines, as discussed above. Therefore, the inventive method pertains to increasing, or attenuating the decrease of, the number of CD4+ T-cells (typically by assaying for the CD4+/CD8+ ratio) within an HIV+ patient. For example, through periodic measurements, the rate at which a given patient's CD4+ T-cells is declining can be assessed both before and after commencement of therapy in accordance with the inventive method. Favorable application of the method at least slows this rate of decrease, and preferably potentiates actual gain in CD4+ cell number. Similarly, the method can decrease, or attenuate the increase of, viral load (i.e., the titer of circulating HIV) within a patient. Favorable response to the treatment can also be monitored by measuring leukocyte adhesion, lymphocyte trafficking, and monocyte/macrophage mobility (i.e., a chemotaxis assay).

In one embodiment, at least one compound within the pharmacologically-acceptable composition can be a 5-alkyl-resorcinol derivative. Such compounds are advantageous for use in the inventive method as they generally exhibit low cytotoxicity (see, e.g., U.S. Patent 5,859,067). Exemplary 5-alkyl-resorcinols can have the following formula:



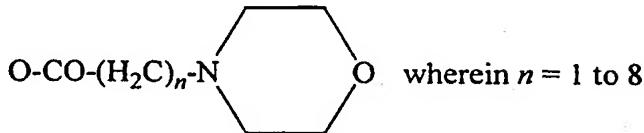
Formula I

wherein,

R¹ is: a) H,

5 b) a C₁₋₄ alkyl group or ester thereof,
 c) COOH,
 d) OH,
 e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di-
 methylamino or ethylamino groups,
 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
 g)

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h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative; or
 i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

20

R² is: a) H, OH or a halogen
 b) C₁₋₆ carboxy or alkoxy group, or
 c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

25

R³ is: a) (W)_m-Y-(Z)_n, wherein

30

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

35

Y is a bond, O, S, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
 ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

5

m and *n* are the same or different, and each is either 0 or 1,

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b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

15

R^4 is: a) H,
b) OH,
c) C_{1-6} alkoxyl or carboxyl

R^5 is: H or OH; and

R^6 is: a) H or OH;

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b) C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof.

c) O-C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof, or

d) a pryenyl, geranyl, or farnesyl group, optionally substituted at any position with one or more halogens,

e) $(W)_m \cdot Y \cdot (Z)_n$, wherein

25

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen.

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS.

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring.

30

ii) CN_{1-3} , CO_2H , or $\text{CO}_2\text{C}_{1-4}\text{ alkyl}$, CONH_2 , $\text{CONHC}_{1-4}\text{ alkyl}$, or $\text{CON}(\text{C}_{1-4}\text{ alkyl})_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different; or

35

iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

- f) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
- g) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different.

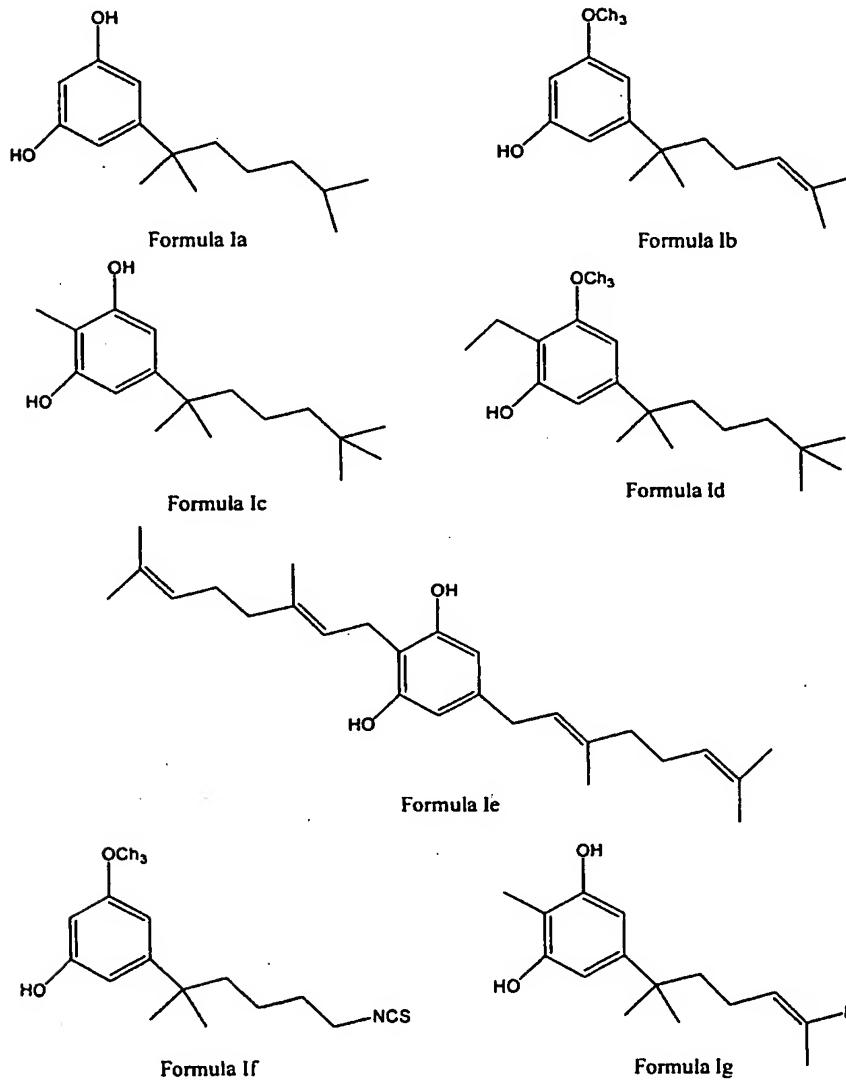
10 Compounds according to Formula I preferably include OH or OCH₃ as R¹ substituents. Preferred substituents at R² are hydrogen, hydroxyl, or methoxyl groups. Where compounds of formula I are included, preferably R⁶ is methyl or ethyl. A more preferred compound according to Formula I has hydroxyl substituents at R¹, R⁵, and a methyl substituent at R⁶; even more preferably, the compound has a third hydroxyl substituent at R². Preferred substituents at R³ are discussed elsewhere herein; however, the invention provides compounds according to Formula I, wherein R³ is:

a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

20 Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,
 Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
 ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different,
 30 wherein at least one of W and Z includes a branched chain and wherein *m* and *n* are the same or different, and each is either 0 or 1,
 b) a terminally-branched C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
 c) a terminally-branched C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄.

alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different. Many such compounds exhibit antineoplastic activity and can be employed as such, as described herein. While any such compounds can be included within the composition in accordance with the inventive method, some preferred compounds are as follows:

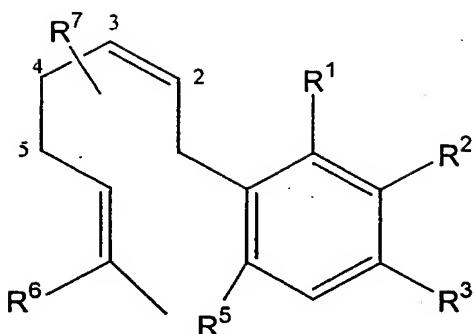


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As mentioned, compounds according to Formula I can have geranyl substituents at R⁶. In this regard, at least one compound within the pharmacologically-acceptable composition can be cannabigerol or a derivative thereof having the following formula:

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Formula II

wherein:

R¹ is: a) H,

b) a C₁₋₄ alkyl group or ester thereof

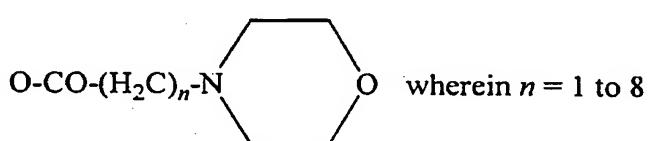
c) COOH,

d) OH,

e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di-methylamino or ethylamino groups,f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,

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g)



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h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative; or

20

i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

25

R² is: a) H, OH or a halogen

b) C₁₋₆ carboxy or alkoxy group, orc) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded,

comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,

5 optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,

optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

10 ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

15 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can

be the same or different, and wherein

m and n are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different,

c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

R⁵ is a) H

b) a C₁₋₄ alkyl group

c) COOH

d) OH, or

e) a O-C₁₋₅ alkyl (ether) or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group;

R⁶ is:

a) hydrogen,

35 b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl (preferably ethyl), or C₁₋₆ haloalkyl,

c) CN,

d) CO₂H,

- e) $\text{CO}_2\text{-C}_{1-4}$ alkyl,
- f) C(Y)(Z)-OH ,
- g) C(Y)(Z)-O-C_{1-4} alkyl, or
- h) C_{1-6} alkyl- $\text{CO}_2\text{-Y}$,

5 wherein Y and Z are each independently H or C_{1-6} alkyl,

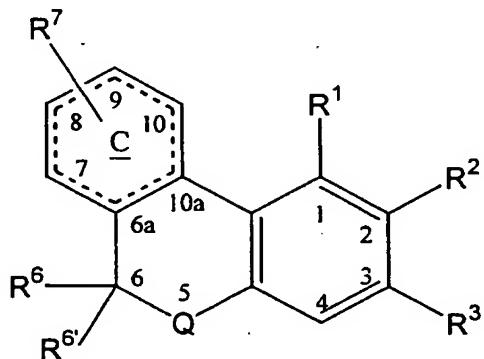
R^7 is:

- a) hydroxy (preferably β -hydroxy) or lactone,
- b) halo,
- c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
- d) CN,
- 10 e) N_3 ,
- f) CO_2H ,
- g) $\text{CO}_2\text{-C}_{1-4}$ alkyl,
- h) C(Y)(Z)-OH ,
- i) C(Y)(Z)-O-C_{1-4} alkyl,
- j) C_{1-6} alkyl- $\text{CO}_2\text{-Y}$, or
- 15 k) =O or =S,

wherein Y and Z are each independently H or C_{1-6} alkyl, and wherein R^7 can be at any of positions 2-5.

Compounds according to Formulas I and II can be synthesized using known procedures from commercially available starting materials (see, e.g., Dominianni et al., *J. Org. Chem.*, 42, 344-46 (1977); Baek et al., *Arch. Pharm. Res.*, 19, 228-30 (1996); Guthrie et al., *J. Org. Chem.* 47, 2369-76 (1982)). For example, acid catalyzed condensation of 2,6-dimethoxyphenol with OH- R^3 can produce a 4-alkylphenol intermediate. Conversion of the phenolic group to the diethylphosphate ester followed by reduction with lithium metal in liquid ammonia can then produce a dimethoxybenzene derivative. Mono- or didemethylation of this compound (e.g., with boron tribromide) can then yield the desired methoxyphenol and/or resorcinol (Formula I), respectively. Compounds of Formula I having alkyl substituents at R^6 can be prepared, for example, first by lithiation of the dimethoxybenzene derivative at R^6 (e.g., in the presence of Bu/THF) and subsequent exposure to an alkylating agent (e.g., methyl or ethyl iodide or sulfate). Mono- or didemethylation of this compound (e.g., with boron tribromide) can then yield the desired methoxyphenol and/or resorcinol (Formula I), respectively, having the alkyl substituents at R^6 . Compounds of Formula II can be prepared, for example, by acid catalyzed condensation of a methoxyphenol and/or resorcinol (Formula I) having a desired substituents at R^3 with geraniol (e.g., in the presence of BF_3 , Et_2O , silica, and CH_2Cl_2). Of course, these compounds can be synthesized by other appropriate methods, many of which are known in the art.

In another embodiment, at least one compound within the pharmacologically-acceptable composition is a cannabinol derivative having the following formula:

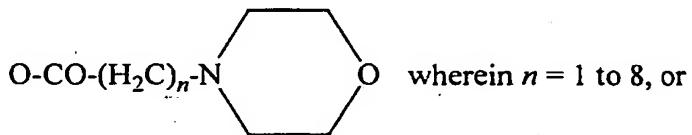


Formula III

wherein,

R¹ is: a)

- a) H,
- b) a C₁₋₄ alkyl group or ester thereof,
- c) COOH,
- d) OH,
- e) a O-C₁₋₅ alkyl (ether) or alkanoyl, optionally substituted by mono- or di-methylamino or ethylamino groups,
- f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
- g)



h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R² is: a) H, OH, or a halogen

b) C₁₋₆ carboxy or alkoxy (preferably methoxy) group, or

c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅₋, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

5 R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

10 Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

15 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

20 m and n are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

25 c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

30 R⁶ and R^{6'} together form =O or =S, or each is independently selected from the group consisting of:

a) hydrogen,

b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,

c) CN,

d) CO₂H,

e) CO₂-C₁₋₄ alkyl,

f) C(Y)(Z)-OH,

35 g) C(Y)(Z)-O-C₁₋₄ alkyl, and

h) C₁₋₆ alkyl-CO₂-Y,

wherein Y and Z are each independently H or C₁₋₆ alkyl,
R⁷ is: a) hydroxy or lactone,
b) halo,
c) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,
d) CN,
e) N₃,
f) CO₂H,
g) CO₂-C₁₋₄ alkyl,
h) C(Y)(Z)-OH,
i) C(Y)(Z)-O-C₁₋₄ alkyl,
j) C₁₋₆ alkyl-CO₂-Y, or
k) =O or =S,
wherein Y and Z are each independently H or C₁₋₆ alkyl;
Q is: a) O or S, or
b) N-W, wherein W is:
i) hydrogen,
ii) C₁₋₆ alkoxyalkyl, C₁₋₆ alkyl, or C₁₋₆ haloalkyl
iii) OC₁₋₆ alkyl, or OC₁₋₆ haloalkyl,
iv) CN,
v) C₁₋₆ alkyl,
vi) C(Y)(Z)C₁₋₄ alkyl, or
vii) C₁₋₆ alkyl-CO₂-Z,

wherein Y and Z are each independently H or C₁₋₆ alkyl.

It is known in the art that some compounds according to Formula III are

psychoactive, chiefly via agonism of the CB1 receptor. This, in some applications, it may be preferable to employ substituents within Formula III (e.g., of R¹-R⁷, Q, and ring C) that preferably promote CB2 agonist activity, rather than CB1 activity, and are more preferably substituents that promote selective CB2 agonist activity. In some embodiments, to mitigate or eliminate psychoactive effects attributed to some cannabinoids, the inventive method employs a selective CB2 agonist, which is one that preferentially acts on the CB2 receptor, as opposed to the CB1 receptor. Most preferably, the selective CB2 agonist does not bind the CB1 receptor at concentrations in which it activates the CB2 receptor. Various selective CB2 agonists are known in the art. Examples of such compounds include classical and nonclassical cannabinoids, bicyclic cannabinoids, aminoalkylindoles, and eicosanoids (see, e.g., Pertwee, *Pharmacol. Ther.*, 74(2), 129-80 (1997)). To assess whether a given compound is a selective CB2 agonist, its relative affinity for the CB2 and CB1 receptors can be assessed using any suitable method, for example using cells engineered to express the

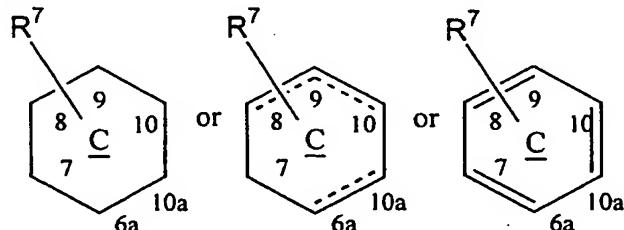
receptors (Ross et al., *Br. J. Pharmacol.*, 126, 665-72 (1999)). Such values typically are expressed as a binding constant, K_i , from which a ratio of K_{i-CB1}/K_{i-CB2} can be calculated. Desirably, the selective CB2 agonist has a K_i for the CB2 receptor of from about 100 nM to about 0.1 nM, preferably from about 25 nM to about 0.2 nM, such as
5 from about 15 nM to about 0.5 nM. Moreover, the ratio of K_{i-CB1}/K_{i-CB2} is at least about 1.5, and more preferably at least about 5 (e.g., at least about 10). Many compounds are known to have suitable CB2 selectivity for use as a CB2 agonist in the inventive method. For example, JWH-015 has a K_{i-CB2} of 13.8 ± 4.6 nM and a K_{i-CB1}/K_{i-CB2} ratio of 27.5; WIN-55,212-2 has a K_{i-CB2} of $.028 \pm 0.16$ nM and a K_{i-CB1}/K_{i-CB2} ratio of 6.75;
10 5-F Δ B-THO has a K_{i-CB2} of 8.7 ± 3.5 nM and a K_{i-CB1}/K_{i-CB2} ratio of 6.55; JWH-018 has a K_{i-CB2} of 2.94 ± 2.65 nM and a K_{i-CB1}/K_{i-CB2} ratio of 3.23; CP-56,667 has a K_{i-CB2} of 23.6 ± 6.5 nM and a K_{i-CB1}/K_{i-CB2} ratio of 2.61; L759656 has a K_{i-CB2} of 11.8 ± 2.5 nM and a K_{i-CB1}/K_{i-CB2} ratio of 414.24; and L759633 has a K_{i-CB2} of 6.4 ± 2.2 nM and a K_{i-CB1}/K_{i-CB2} ratio of 162.97 (see above-referenced references). It is within the ordinary skill in the art to assess these values for yet-unmeasured (or novel) compounds. Aside from binding the CB2 receptor preferentially, a preferred selective CB2 agonist exhibits greater CB2-directed physiological response than CB1 response. A classic assay for differential activity measures the ability of a compound to inhibit drug-induced cyclic AMP (cAMP) production in cells engineered to express the respective receptor,
15 typically expressed as EC₅₀ (a percentage of maximal effects) (Ross et al., *Br. J. Pharmacol.*, 126, 665-72 (1999)). Preferably, selective CB2 agonist typically exhibits a EC_{50-CB2}/EC_{50-CB1} ratio of greater than about 10, more typically greater than about 100 (e.g., greater than about 500). Many compounds are known to have suitable CB2 selectivity, and thus can be used as a CB2 agonist in the inventive method. For
20 example, L759656 has an EC_{50-CB2}/EC_{50-CB1} ratio of >3000; and L759633 has a EC_{50-CB2}/EC_{50-CB1} ratio of >1000. It is within the ordinary skill in the art to assess these values for yet-unmeasured (or novel) compounds.
25

For CB2 selectivity, R¹ in Formula III preferably is not OH, as it is in the natural cannabinol and tetrahydrocannabinol compounds. Rather, preferably R¹ in Formula III is H, O-C₁₋₄ alkyl (more preferably methoxy) or a hemi ester of succinic acid, malonic acid or the alaninate ester of alanine and salts thereof. In another preferred embodiment, R¹ and R² together comprise a substituent of the formula -O(CH₂)₃₋₅-, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprise a ring where at least one hydrogen atom thereof is optionally substituted with a halogen (e.g., an O₂ propano ring). Furthermore, where R² in Formula III is a halogen, preferably it is iodo. Preferably, R⁶ and R^{6'} together form =O or each are methyl, ethyl, or methoxy.
30
35

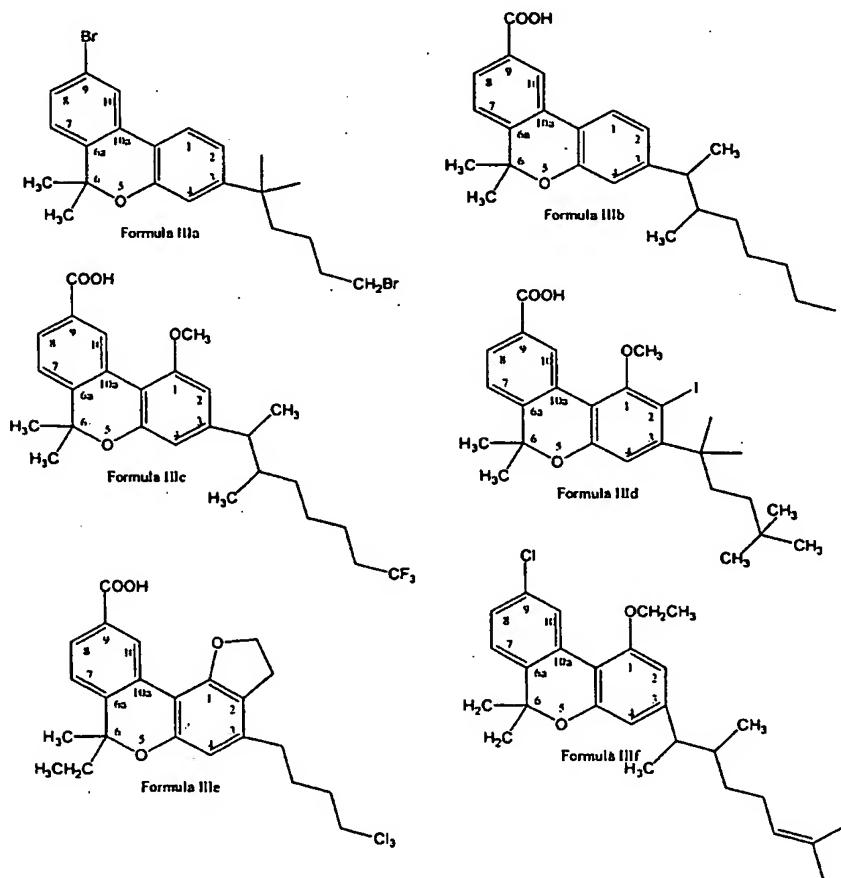
While R⁷ can be at any of positions 7-10 of ring C, preferably it is at position 9 of the ring. Where it is desired to promote CB2 selectivity, R⁷ preferably is electronegative

(e.g., COOH, halogen, β -hydroxy, or lactone.), and to enhance activity, it can be substituted with either a lactone or a β -hydroxy group.

Ring C in Formula III can be any of the following (the dashed lines representing a double bond at either the Δ 6a-10a, Δ 8-9, or Δ 9-10 position):



5 However, to promote CB₂ selectivity, preferably the ring is aromatic. In this regard, a preferred embodiment of the invention provides novel anti-viral cannabinol derivatives according to Formula III, wherein ring C is aromatic. In such compounds, R⁷ preferably is electronegative and more preferably is on C9. Furthermore, R¹ preferably is other than OH and preferably is deoxy, an ester, or an ether. Exemplary cannabinol derivative
10 compounds include:

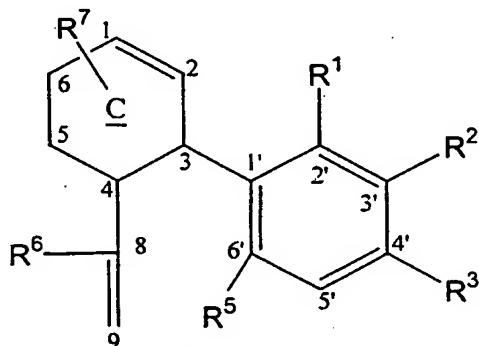


Many compounds according to Formula III are well known, and others can be manufactured in accordance with published methods (see, for example, International Patent Application WO99/20268 (Burstein), and U.S. Patents 2,509,386 (Adams), 3,799,946 (Loev), 3,856,821 (Loev), 3,897,306 (Vidic et al.), 4,064,009 (Fukada et al.), 4,087,545 (Archer et al.), 4,142,139 (Bindra), 4,309,545 (Johnson), 4,599,327 (Nógrádi et al.), 4,833,073 (McNally et al.), 4,876,276 (Mechoulam et al.), 4,973,603 (Burstein), 5,338,753 (Burstein et al.), 5,389,375 (ElSohly), 5,440,052 (Makriyannis et al.), 5,605,906 (Lau), and 5,635,530 (Mechoulam et al.); and Charalambous et al., *Pharm. Biochem. Behav.*, 40, 509-12 (1991), Gareau et al., *Bioorg. Med. Chem. Lett.*, 6(2), 189-10 94 (1996), Griffin et al., *Br. J. Pharmacol.*, 126, 1575-84 (1999), Huffman et al., *Bioorg. Med. Chem. Lett.*, 6, 2281-88 (1998), Lemberger et al., *Clin. Pharmacol. Ther.*, 18(6), 720-26 (1975), Loev et al., *J. Med. Chem.*, 16(11), 1200-06 9 (1973), Loev et al., *J. Med. Chem.*, 17(11), 1234-35 (1974), Martin et al., *Pharm. Biochem. Behav.*, 46, 295-15 301 (1993), Papahatjis et al., *J. Med. Chem.*, 41(7), 1195-1200 (1998), Pars et al., *J. Med. Chem.*, 19(4), 445-53 (1976), Pertwee et al., *Pharmacol. Ther.*, 74(2), 129-80 (1997), Razdan et al., *J. Med. Chem.*, 19(4), 454-60 (1976), Razdan, *Pharmacol. Reviews*, 38(2) 75-149 (1980), Reggio et al., *J. Med. Chem.*, 40(20), 3312-18 (1997), Reggio et al., *Life Sci.*, 56(23/24), 2025-32 (1995), (Ross et al., *Br. J. Pharmacol.*, 126, 665-72 (1999), Thomas et al., *J. Pharm. Exp. Ther.*, 285(1), 285-92 (1998), Wiley et al., 20 *J. Pharm. Exp. Ther.*, 285(1), 995-1004 (1998), Winn et al., *J. Med. Chem.*, 19(4), 461-71 (1976), and Xie et al., *J. Med. Chem.*, 41, 167-74 (1998)).

In the preferred embodiment wherein ring C of Formula III is aromatic, such compounds additionally can be manufactured by aromatizing an appropriate tetrahydrocannabinol (THC) derivative molecule by known methods (see, e.g., Adams et al., *J. Am. Chem. Soc.*, 62, 23401 (1940); Ghosh et al., *J. Chem. Soc.*, 1393 (1940); and Adams et al., *J. Am. Chem. Soc.*, 70, 664 (1948)). For example, aromatization of such compounds can occur by heating the compound with sulfur at about 238-240 °C, under a nitrogen atmosphere, for about 4 hours (Rhee et al., *J. Med. Chem.*, 40(20), 3228-33 (1997)). Other suitable methods include aromatization using a catalyst (e.g., palladium on carbon) or a chemical dehydrogenating agent (e.g., 2,3-dichloro-5,6-dicyanoquinone) (see, for example, U.S. Patent 3,799,946 (Loev)).

As mentioned, in some applications of the inventive method, particularly where at least one of the compounds within the composition is a cannabinol derivative, it is desirable to mitigate potentially deleterious psychoactivity attributed to some such compounds. As an alternative to employing non-psychotropic cannabinol derivatives (e.g., selective CB2 agonists) within the composition, other pharmacologically-active agents can be employed in addition to mitigate psychoactive effects. For example, as some of the aforementioned compounds might exert some activity on CB1 receptors, it

is often desirable to adjunctively administer a selective CB1 antagonist to the patient. Indeed, in some applications it is desired to co-administer a non-selective CB2 agonist (e.g., Δ 8- or Δ 9-THC and derivatives thereof) in small doses, in which cases administration of a CB1 antagonist is preferred. Many suitable selective CB1 antagonists are known in the art (Rinaldi-Carmona et al., *FEBS Lett.*, 350, 240-44 (1994), see also U.S. Patents 5,624,941 (Barth et al.), 5,747,524 (Cullinan et al.), 5,925,768 (Barth et al.)). SR-1241716A is a particularly potent, and theretofore preferred, selective CB1 antagonist for use in the inventive method. Other preferred selective CB1 antagonists are cannabidiol and its derivatives (see, e.g., U.S. Patent 2,304,669 (Adams); Razdan et al., *Pharmacol. Reviews*, 38(2), 75-149 (1986); Reggio et al., *Life Sci.*, 56(23-24), 2025-32 (1995)), as these potently antagonize the CB1 receptor. In addition to antagonizing CB1, cannabidiol and many of its derivatives also advantageously attenuate the cytochrome P₄₅₀ system in the liver, leading to enhanced bioavailability of other compounds within the composition (e.g., Bornheim et al., *Chem. Res. Toxicol.*, 11, 1209-16 (1998)). In this regard, in some embodiments of the inventive method, at least one compound within the pharmacologically-acceptable composition is cannabidiol or a derivative thereof having the following formula:

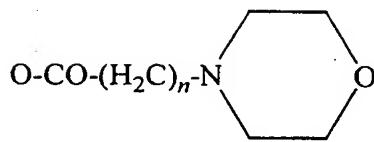


wherein:

R¹ is: a) H,
 b) a C₁₋₄ alkyl group or ester thereof
 c) COOH,
 d) OH,
 e) a O-C₁₋₅ alkyl (preferably methoxy) or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,
 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,

20

g)



wherein $n = 1$ to 8, or

5 h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of
10 the carboxyl terminated derivative;

i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

15 R² is: a) H, OH or a halogen
b) C₁₋₆ carboxy or alkoxy group, or
c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded,
comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.
20

R³ is: a) (W)_m-Y-(Z)_n, wherein
W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,
optionally substituted with at least one halogen,
Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,
25 Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,
optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄
alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the
amide nitrogen can be the same or different, or
30 iii) a phenyl or benzyl group, optionally substituted with
halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyltio, CN, CF₃, CO₂H, or
CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄
alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can
be the same or different, and wherein
35

m and n are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄

alkyl, or $\text{CON}(\text{C}_{1-4}\text{ alkyl})_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different,

5 c) a C_{5-12} alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN_{1-3} , NCS , CO_2H , or $\text{CO}_2\text{C}_{1-4}$ alkyl, CONH_2 , CONHC_{1-4} alkyl, or $\text{CON}(\text{C}_{1-4}\text{ alkyl})_2$, wherein each C_{1-4} alkyl on the amide nitrogen can be the same or different;

10 R^5 is a) H
 b) a C_{1-4} alkyl group
 c) COOH
 d) OH , or
 e) a O-C_{1-5} alkyl (ether) or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group;

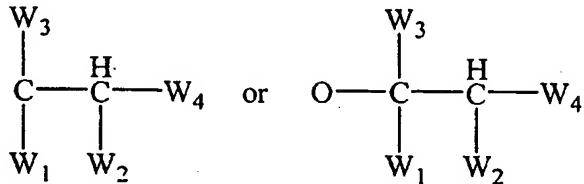
15 R^6 is:
 a) hydrogen,
 b) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
 c) CN ,
 d) CO_2H ,
 e) $\text{CO}_2\text{-C}_{1-4}$ alkyl,
 f) C(Y)(Z)-OH ,
 g) C(Y)(Z)-O-C_{1-4} alkyl, or
 h) C_{1-6} alkyl- $\text{CO}_2\text{-Y}$,
 wherein Y and Z are each independently H or C_{1-6} alkyl,

20 R^7 is: a) hydroxy or lactone,
 b) halo,

25 c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, C_{1-6} carboxy, or C_{1-6} haloalkyl,
 d) CN ,
 e) N_3 ,
 f) CO_2H ,
 g) $\text{CO}_2\text{-C}_{1-4}$ alkyl,
 h) C(Y)(Z)-OH ,
 i) C(Y)(Z)-O-C_{1-4} alkyl,
 j) C_{1-6} alkyl- $\text{CO}_2\text{-Y}$, or
 k) $=\text{O}$ or $=\text{S}$,

30 wherein Y and Z are each independently H or C_{1-6} alkyl, and wherein R^7 can be at any of positions 1, 2, 5, or 6 of ring C.

In addition to having the indicated substituents, R³ in any of formulas I-IV preferably is:



5 wherein W₁ is H, methyl, or ethyl, wherein W₂ and W₃ are each independently H or methyl, wherein at least one of W₁, W₂, and W₃ is other than H and/or halogenated, and wherein W₄ is a C₁₋₄ alkyl or haloalkyl, optionally substituted with an aromatic ring. Preferably, R³ is a branched C₆₋₁₂ alkyl group containing at least one double bond (more preferably at position C_{4-C₁₀}), and preferably the chain has an odd number of carbon atoms. More preferably, R³ is terminally branched or contains a terminal double bond, and the invention provides compounds according to Formulas I-IV having such substituents. More preferably, R³ preferably is dimethylheptyl (DMH) (e.g., 1',1' DMH or 1'R, 2'S DMH), dimethylhexyl, or dimethylpentyl. For example, R³ can be a di-, tri-, or tetramethylpentyl, -hexyl, or -heptyl, etc., chain (e.g., 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl). In some instances, the R³ substituent can have bulky terminal moieties, for example, methyl, dimethyl, (CH₂)₁₋₆-CON(CH₃)₂, or C₆₋₁₂ haloalkyl with halogenated terminal carbon atoms (preferably bromine).

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In the context of this invention, halogenated alkanes, alkenes, and alkynes can have any number of halogen substitutions. In a preferred embodiment, the halogenated alkane, alkene, or alkyne has at least one halogen on a terminal carbon atom (e.g., CX₁₋₃, where X is halogen). Alkyl groups (as well as alkenes and alkynes) can be straight chain or branched. Moreover, the compounds can exist as a single stereoisomer or a mixture of stereoisomers (e.g., a racemic mixture), or a single geometric isomer (e.g., E, Z, cis or trans) or a mixture of geometric isomers, all of which are within the scope of the invention.

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In carrying out the inventive method, the composition can be delivered to a patient in any amount and over any time course suitable for producing the desired therapeutic effect, and one of skill in the art will be able to determine an acceptable dosing schedule. For example, where the method is employed to treat HIV disease, an optimal dosage can be assessed by assaying the number of circulating viral particles (viral load) and/or CD4+ cell count in response to increasing dosage. Typically, the composition is delivered to a patient between 1 and about 6 times a day, if not continuously through transdermal or time release formulations. However, in some

30

applications. it is appropriate to administer the composition less often. Generally each dose is between about 2 mg/m³ to about 1000 mg/m³, and more preferably about 0.01 mg/kg/day, about 1 mg/kg/day, such as about 10 ng/kg/day to about 10 mg/kg/day, and can be up to about 100 mg/kg/day (e.g., about 250 mg/kg/day). These dosages can be
5 somewhat reduced when the composition is employed in combination with other agents, and especially when the cytochrome P₄₅₀ system is attenuated (e.g., through cannabidiol derivatives); as discussed herein. Moreover, where a selective CB1 antagonist is employed, it can be administered in the same dose or composition as the inventive
10 composition or in a different formulation or dosing schedule. In some applications, it is preferable to begin administering the selective CB1 antagonist prior to (e.g., at least 1-4 days prior to) the composition, to further minimize any residual activation of the CB1 receptor and to prevent degradation of the compound(s) within the composition. Of course, as some patients can develop tolerance to one or more compounds within the
15 composition over the course of treatment, the dosage amount and/or schedule can be adjusted as appropriate. Moreover, the dosage amount and schedule can be reduced as a patient responds favorably to treatment and/or if any toxic side effects are noted.

By virtue of its many effects, the method can be employed to treat many diseases or disorders associated with immune dysfunction in addition to HIV disease. For example, the method can treat autoimmune diseases (e.g., systemic lupus-erythematosus, Hashimoto's thyroiditis, myasthenia gravis, rheumatoid arthritis, multiple sclerosis, Guillan-Barre syndrome, glomerulonephritis, etc.). The method can also treat diseases causing or depending on inflammatory conditions (e.g., Crohn's disease, ulcerative colitis, forms of asthma), and it is particularly effective in combating many neoplastic diseases, microbial (e.g., mycobacterial, fungal) infections, or viral
20 infections, especially HSV, Epstein-Barr virus, Cytomegalovirus, HIV, and hepatitis B and C). The method also can treat abnormal immune responses, abnormal scar formation (e.g., surgical adhesions or keloids), allograft rejection, atherosclerosis and associated heart diseases. Of course, the patient can be any sort of animal (e.g., a monkey, cat, dog, horse, cow, pigs, goat, and sheep, etc.).

30 Of course, where the method is employed to combat a disease associated with immune dysfunction, other appropriate therapeutic agents can be adjunctively employed as well. For example, the method can include the adjunctive administration of antineoplastics, antitumor agents, antibiotics, antifungals, antivirals (particularly antiretroviral compounds), antihelminthic, and antiparasitic compounds. Exemplary
35 antiviral agents suitable for adjunctive use in the inventive method include abacavir, azidothymidine cidofovir, delavirdine mesylate, didanosine, dideoxycytidine, efavirenz, foscarnet, ganciclovir, indinavir sulfate, lamivudine, nelfinavir mesylate, nevirapine, ritonavir, saquinavir, saquinavir mesylate, stavudine, zalcitabine, etc. In treating tumors

or neoplastic growths, suitable adjunctive compounds can include anthracycline antibiotics (such as doxorubicin, daunorubicin, carinomycin, N-acetyladriamycin, rubidazone, 5-imidodaunomycin, and N-acetyl daunomycin, and epirubicin) and plant alkaloids (such as vincristine, vinblastine, etoposide, ellipticine and camptothecin),
5 paclitaxel and docetaxol, mitotane, cisplatin, phenesterine, etc. Anti-inflammatory therapeutic agents suitable for adjunctive use in the present invention include steroids and non-steroidal anti-inflammatory compounds, (such as prednisone, methylprednisolone, paramethazone, 11-fludrocortisol or fluorocortisone, triamcinolone, betamethasone and dexamethasone, ibuprofen, piroxicam, beclomethasone;
10 methotrexate, azaribine, etretinate, anthralin, psoralins); salicylates (such as aspirin; and immunosupresant agents such as cyclosporine). Additional pharmacologic agents suitable for adjunctive use in the inventive method include anesthetics (such as methoxyflurane, isoflurane, enflurane, halothane, and benzocaine); antiulceratives (such as cimetidine); antiseizure medications (such as barbituates; azothioprine (an
15 immunosuppressant and antirheumatic agent); and muscle relaxants (such as dantrolene and diazepam). Moreover, the method can be employed in conjunction with specific antibody therapies or steroid therapies in treating autoimmune diseases. Other pharmacologically-active agents that can be adjunctively employed in conjunction with the composition include other constituents of natural marijuana having antimicrobial or
20 anti-inflammatory activities (e.g., cannabigerol and its derivatives, cannabichromine and its derivatives, cannabinolic acid and its derivatives, cannabidiolic acid and its derivatives, terpenoids, flavonoids (e.g., cannflavin), etc.).

The composition can include biologically active agents, such as lymphokines or cytokines, anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchoacting, local anesthetic, immunomodulating, enzymatic, hormonal, growth promoting and regenerating agents, as well as neurotransmitters, and cell receptor proteins and ligands, among many other agents. Examples of other biological agents are analgesics (such as acetaminophen, anileridine, aspirin, buprenorphine, butabital, butorphanol, choline
25 salicylate, codeine, dezocine, diclofenac, diflunisal, dihydrocodeine, elcetonin, etodolac, fenoprofen, hydrocodone, hydromorphone, ibuprofen, ketoprofen, ketorolac, levorphanol, magnesium salicylate, meclofenamate, mefenamic acid, meperidine, methadone, methotrimeprazine, morphine, nalbuphine, naproxen, opium, oxycodone,
30 oxymorphone, pentazocine, phenobarbital, propoxyphene, salsalate, sodium salicylate, tramadol and narcotic analgesics in addition to those listed above). Anti-anxiety agents are also useful including alprazolam, bromazepam, buspirone, chlordiazepoxide, clormezanone, clorazepate, diazepam, halazepam, hydroxyzine, ketazolam, lorazepam, meprobamate, oxazepam and prazepam, among others. Other biologically-

active agents include anti-anxiety agents associated with mental depression, such as chlordiazepoxide, amitriptyline, loxapine, maprotiline, and perphenazine, among others. Examples of other active ingredients include anti-inflammatory agents such as non-rheumatic aspirin, choline salicylate, diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, lidomide, magnesium salicylate, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, salsalate, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid, thalidomide, linomide, and tolmetin, as well as anti-inflammatories for ocular treatment (such as diclofenac, flurbiprofen, indomethacin, ketorolac, and rimexolone generally for post-operative treatment)), and anti-inflammatories for non-infectious nasal applications (such as beclomethaxone, budesonide, dexamethasone, flunisolide, triamcinolone, and the like); soporifics (anti-insomnia/sleep inducing agents) such as those utilized for treatment of insomnia, including alprazolam, bromazepam, diazepam, diphenhydramine, doxylamine, estazolam, flurazepam, halazepam, ketazolam, lorazepam, nitrazepam, prazepam quazepam, temazepam, triazolam, zolpidem and sopolclone, among others; sedatives including diphenhydramine, hydroxyzine, methotripteneprazine, promethazine, propofol, melatonin, tripteneprazine, and the like; sedatives and agents used for treatment of petit mal seizures and tremors, among other conditions, such as amitriptyline HCl; chlordiazepoxide, amobarbital; secobarbital, aprobarbital, butabarbital, ethchlorvynol, glutethimide, L-tryptophan, mephobarbital, methohexitol sodium salt, midazolam HCl, oxazepam, pentobarbital Na, Phenobarbital, secobarbital sodium salt, thiambutal sodium, and many others. Other active compounds can include agents used in the treatment of head trauma (brain injury/ischemia), such as enadolene HCl (e.g., for treatment of severe head injury), cytoprotective agents, and agents for the treatment of menopause, menopausal symptoms (treatment), e.g., ergotamine, belladonna alkaloids and phenobarbital, for the treatment of menopausal vasomotor symptoms, e.g., clonidine, conjugated estrogens and medroxyprogesterone, estradiol, estradiol cypionate, estradiol valerate, estrogens, conjugated estrogens, esterified estrone, estropipate, and ethinyl estradiol. Examples of agents for treatment of pre menstrual syndrome (PMS) are progesterone, progestin, gonadotrophic releasing hormone, oral contraceptives, danazol, luprolide acetate, vitamin B6; agents for treatment of emotional/psychiatric treatments such as tricyclic antidepressants including amitriptyline HCl (Elavil), amitriptyline HCl, perphenazine (Triavil) and doxepin HCl (Sinequan). Examples of tranquilizers, anti-depressants and anti-anxiety agents are diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax), SSRI's (selective Serotonin reuptake inhibitors), fluoxetine HCl (Prozac), sertraline HCl (Zoloft), paroxetine HCl (Paxil), fluvoxamine maleate (Luvox) venlafaxine HCl (Effexor), serotonin, serotonin agonists (Fenfluramine); antibiotics (e.g., fluoroquinolones and

tetracycline); antihistamines; catabolic steroids; and vasoactive agents (e.g., beta-blockers and pentoxiphylline (Trental)). Other compounds include cannabinoids such as CT-3 and HU-210.

As mentioned, for use in the inventive method, the compound(s) are incorporated
5 into a pharmacologically-acceptable composition including a suitable carrier, and
optionally other inactive or active ingredients. Such compositions are suitable for
delivery by a variety of commonly-employed routes of delivery, such as, for example,
buccal, sublingual, dermal, intraocular, intraotical, pulmonary, transdermal,
intralymphatic, intratumor, intracavitory, intranasal, subcutaneous, implantable,
10 inhalable, intradermal, rectal, vaginal, transmucosal, intramuscular, intravenous and
intraarticular routes, among many others. Depending on the desired manner of
application, the composition can include adjuvants, bile salts, biodegradable polymers
and co-polymers, buffers, chelating agents, colorants, diluents, emollients, emulsifiers,
enzyme inhibitors, hydrogels, hydrophilic agents, lipoproteins and other fatty acid
15 derivatives, liposomes and other micelles, microporous membranes, mucoadhesives,
neutral and hydrophobic polymers and co-polymers, particulate systems, perfumes, salt
forming acids and bases, semi-permeable membranes, single or multiple enteric
coatings, solvents (e.g., alcohols, dimethyl sulfoxide (DMSO), etc.), surfactants, viral
envelope proteins, or other ingredients.

20 In one of its forms, the composition can be an inhalable formulation comprising
an aerosol of liquid or solid particles, such as are known in the art. Application of the
composition via inhalation can treat bronchial conditions associated with inflammation
(e.g., the common cold (rhinovirus), influenza, cystic fibrosis, etc.). This formulation
can further comprise additional agents such as preservatives, antioxidants, flavoring
25 agents, volatile oils, buffering agents, dispersants, surfactants, and the like, as are known
in the art. Such formulation can also be provided with an inhalant, or in the inhalant,
either in unit form or in a form which permits its repetitive use.

The composition can also be a topical formulation (e.g., ointment, cream, lotion,
30 paste, gel, spray, aerosol oil, etc.), wherein the carrier is a diluent for the agent suitable
for topical delivery, e.g., petrolatum, lanoline, polyethylene glycols, alcohols and the
like, optionally including trans-dermal enhancers. In the topical formulation, the carrier
may be in a form suitable for formulating creams, gels, ointments, sprays, aerosols,
patches, solutions, suspensions and emulsions.

35 The composition can also be formulated for oral delivery, for example in the
form of capsules, cachets, lozenges, tablets, powder, granules, solutions, suspensions,
emulsions, essential oils (particularly hemp seed oil), etc. Such formulations typically
include aqueous or non-aqueous liquid solutions and suspensions (e.g., oil-in-water or
water-in-oil emulsions). Such oral formulations typically are encased in an enteric

coating. Examples of oral formulations are buccal or sub-lingual formulation comprising lozenges which can also comprise flavoring agents and other known ingredients, or pastilles which can also comprise an inert base containing, for example, gelatin, glycerin, sucrose, acacia, and other ingredients and fillers as is known to the practitioner.

The composition can also be a parenteral formulation, such as injectable solutions and suspensions. Typically, such formulations also comprise agents such as antioxidants, buffers, anti-bacterial agents, other anti-viral agents such as direct acting inhibitors of replication, and solutes which render the solution or suspension isotonic with the blood of an intended recipient. The solutions or suspensions are typically sterile aqueous or non-aqueous injectable solutions or suspensions, and can also comprise suspending agents and thickening agents. This formulation is generally provided in a sealed ampule or vial.

The composition can also be a slow release formulation, which, when administered or applied to a subject, is capable of releasing a desired amount of the compound(s) over a pre-determined period of time. Alternatively, the composition can be a transdermal formulation, in which the carrier is suitable for facilitating the transdermal delivery of the agent. Examples are aqueous and alcoholic solutions, DMSO, oily solutions and suspensions, and oil-in-water or water-in-oil emulsions. A transdermal formulation can also be an iontophoretic transdermal formulation, in which typically the carrier can be an aqueous and/or alcoholic solution, an oily solution or suspension and an oil-in-water and water-in-oil emulsion. This formulation can further comprise a transdermal transport promoting agent, and be provided in the form of a kit with a transdermal delivery device, preferably an iontophoretic delivery device, many variations of which are known in the art.

Additional formulations of the composition include, but are not limited to an implantable capsule or cartridge (e.g., for tissue implantation), a patch, an implant, or a suppository (e.g., for rectal or transmucosal administration).

Typically, the composition will be distributed, either to physicians or to patients, in an administration kit, and the invention provides such an immunomodulating kit. Typically, such kits include, in separate containers, an administration device (e.g., syringes and needles, inhalators, pills, suppositories, transdermal delivery devices, etc) and a plurality of unit dosages of the composition as described above. In some kits, the composition can be preformulated. Other kits include separate ingredients for formulating the composition. The kit can additionally comprise a carrier or diluent, a case, and instructions for formulating the composition (if applicable) and for employing the appropriate administration device.

As mentioned, compounds according to Formula I have antineoplastic or cytotoxic activity, and the invention provides a method of inhibiting the growth of a neoplasm (e.g., a neoplastic cell or tumor), comprising delivering such a compound to the neoplasm under conditions sufficient for the growth of the neoplasm to be inhibited.

5 Without being bound by any particular theory, 5-alkyl-resorcinols can cause DNA cleavage, which can potentially induce apoptosis within neoplastic cells. In this regard, preferably the alkylated resorcinol derivative is delivered to the neoplasm under conditions sufficient to potentiate apoptosis. The exact dosing schedule needed to induce apoptosis will depend on the type of compound employed, and whether
10 additional compounds are also employed. In this regard, the method can be delivered adjunctively, in conjunction with the delivery of at least one other antineoplastic agent (such as those set forth above).

In many applications, the method is employed *in vivo* (e.g., within a patient), such as within a tumor or blood dyscrasia. In some such *in vivo* applications, the
15 alkylated resorcinol derivative is delivered to the neoplasm by introducing it into systemic circulation, such as through the gastric, intestinal, oral, or rectal wall or via intravenous injection. In still other applications where the neoplasm is or comprises a tumor, the alkylated resorcinol derivative can be delivered by intratumoral injection. Such mode of delivery can, in some instances, increase the potential local concentration
20 of the compound. For such *in vivo* applications, the compound can be formulated into a pharmacologically-acceptable composition as indicated herein, as appropriate.

The method can be employed to combat tumor growth, which, while preferable, need not result in elimination of the tumor or decrease in tumor mass. In this regard, the method can be employed to attenuate tumor growth. Such an effect can, for example,
25 make otherwise resistant neoplastic cells more susceptible to other antineoplastic agents, and the method contemplates the adjunctive use of such other compounds, many of which are known in the art (e.g., aldesleukin, altretamine, amifostine, asparaginase, azathioprine, bicalutamide, bicalutamide, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin injection, cladribine, cyclophosphamide,
30 cyclosporine o, cytarabine, cytarabine liposome injection, dacarbazine, dactinomycin, daunorubicin, denileukin diftitox, dextrazoxane, docetaxel, doxorubicin, doxorubicin hydrochloride, estramustine phosphate sodium, etoposide, etoposide phosphate, floxuridine pegaspargase., fludarabine phosphate, flutamide, gemcitabine HCl, goserelin, granisetron hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide,
35 interferon alfa-2a, recombinant, interferon alfa-2b, irinotecan hydrochloride, leucovorin, leuprolide acetate, levamisole, lomustine, L-PAM, L-phenylalanine mustard, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone hydrochloride, nilutamide, nilutamide, octreotide, ondansetron

hydrochloride, paclitaxel, pamidronate disodium, pentostatin, phenylalanine mustard, plicamycin, polifeprosan 20 with carmustine implant, porfimer sodium, procarbazine HCl, rituximab, sargramostim, streptozocin 2-deoxy-2-[(methylnitrosoamino), tamoxifen citrate, teniposide, testolactone, thioguanine, thiotepa for injection, topotecan hydrochloride, toremifene citrate, trastuzumab, tretinoin, trimetrexate glucuronate, valrubicin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate, etc.). Moreover, even where tumor growth continues, such attenuation is useful for slowing the progress of the disease, thus permitting greater time for other therapeutic approaches. Indeed, combination therapy may allow for smaller or greater doses of other such antineoplastic agents for shorter or longer durations, thus potentially facilitating increased efficacy and potentially reducing side effects.

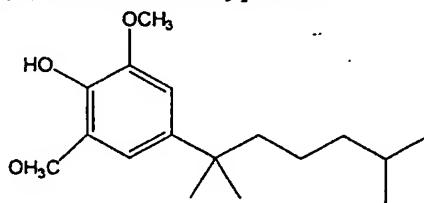
EXAMPLES

While one of skill in the art is fully able to practice the instant invention upon reading the foregoing detailed description, the following examples will help elucidate some of its features. Of course, as these examples are presented for purely illustrative purposes, they should not be used to construe the scope of the invention in a limited manner, but rather should be seen as expanding upon the foregoing description of the invention as a whole.

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EXAMPLE 1

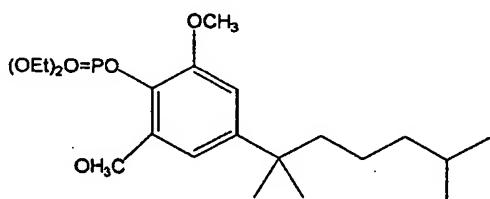
This example demonstrates the synthesis of a compound according to Formula I. A mixture of 2,6-dimethoxyphenol (73.4 g, 0.48 mole), 2,6-dimethyl-2-heptanol (69.0 g, 0.48 mole) and methanesulfonic acid (95 mL) was stirred at 50° C for 3 h and then at room temperature overnight. The mixture was poured over ice-water (600 mL) with stirring. The mixture was extracted with CH₂Cl₂ (2 x 200 mL). The extracts were washed with water, saturated aqueous NaHCO₃, saturated aqueous sodium chloride solution and dried over anhydrous Na₂SO₄. The solution was concentrated under reduced pressure to obtain the product as an oil (130 g, 96%). Analysis of this substance (MS (FAB) m/z 281 (MH)⁺; ¹H NMR (CDCl₃) δ 0.80 (d, 6H), 1.0-1.1 (m, 4H), 1.27 (s, 6H), 1.40-1.60 (m, 3H), 3.89 (s, 6H), 5.36 (s, 1H), 6.54 (s, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol:



EXAMPLE 2

This example demonstrates the synthesis of a compound according to Formula I.

A solution of crude 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol from Example 1 (130 g, 0.46 mole) in dry CCl_4 (100 mL) was cooled in ice-bath and diethyl phosphite (70 mL, 0.54 mole) was added. To the stirred mixture triethylamine (75 mL, 0.54 mole) was added dropwise at such a rate as to maintain the temperature of the reaction mixture below 10 °C. The reaction mixture was stirred in the ice-bath for 2 h and at room temperature overnight. The mixture was then diluted with CH_2Cl_2 (200 mL), washed with water, 4N aqueous NaOH (100 mL), 1N aqueous HCl (125 mL), water and saturated aqueous sodium chloride solution. The extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography over a column of silica using cyclohexane:EtOAc (7:1 to 3:1 gradient) as the eluent to obtain 103 g (54%) of the product as a colorless waxy oil. Analysis of this substance (MS (FAB) m/z 417 (MH^+)). ^1H NMR (CDCl_3) δ 0.81 (d, 6H), 1.0-1.1 (m, 4H), 1.26 (s, 6H), 1.35-1.6 (m, 9H), 3.86 (s, 6H), 4.25-4.38 (m, 4H), 6.53 (s, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenyl diethyl phosphate:



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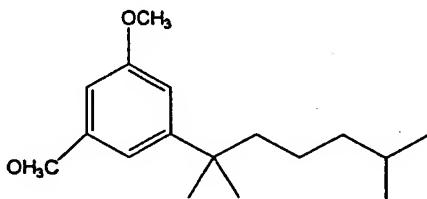
EXAMPLE 3

This example demonstrates the synthesis of a compound according to Formula I.

A solution of 4-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenyl diethyl phosphate from Example 2 (82 g, 0.197 mole) in Et_2O (175 mL) and THF (35 mL) was added slowly to liquid ammonia (450 mL) contained in a 3-neck vessel fitted with mechanical stirrer, thermometer, dry ice condenser and a pressure equalizing addition funnel while adding small freshly cut pieces of lithium wire (2.8 g, 0.40 g-atom) at such a rate as to maintain a blue color. The reaction mixture was stirred further for an hour and then quenched by the addition of saturated aqueous NH_4Cl (22 mL). Ether (220 mL) was added and the ammonia was allowed to evaporate overnight. The residue was treated with water (220 mL). The layers were separated and the ether layer was washed with 4N NaOH (200 mL), water (2 x 200 mL) and saturated aqueous sodium chloride solution. The organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The crude product was purified by chromatography over a column of silica

using cyclohexane:EtOAc (95:5) as the eluent to obtain 43 g (83%) of the product as a colorless oil. Analysis of this substance (MS (FAB) m/z 265 (MH)⁺; ¹H NMR (CDCl₃) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.26 (s, 6H), 1.4-1.6 (m, 3H), 3.79 (s, 6H), 6.30 (m, 1H), 6.49 (m, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene:

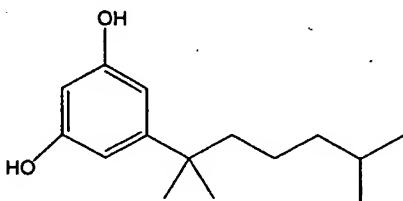
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EXAMPLE 4

This example demonstrates the synthesis of a compound according to Formula I.

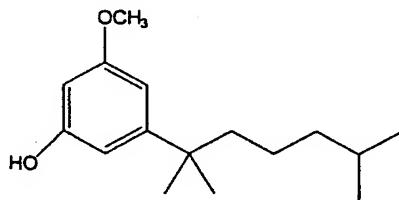
10 A solution of 4-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene from Example 3 (10 g, 0.038 mole) in anhydrous CH₂Cl₂ (100 mL) was cooled in ice-bath and was treated dropwise with a solution of boron tribromide in CH₂Cl₂ (100 mL of 1M solution, 0.10 mole) over a period of 1 h. The mixture was stirred in the cold bath for 2 h and then at room temperature overnight. The reaction mixture was cooled in ice-bath and 15 cautiously treated with water (100 mL). The resulting mixture was diluted with CH₂Cl₂ (100 mL) and treated with half-saturated aqueous sodium bicarbonate solution. The layers were separated, the organic layer was concentrated to half volume under reduced pressure and extracted with 2N aqueous NaOH (2 x 75 mL). The aqueous alkaline extract was cooled and acidified to pH 3.0 with 1N aqueous HCl. The acidified mixture 20 was extracted with Et₂O (2 x 100 mL). The ether layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product thus obtained was purified by chromatography over a column of silica using cyclohexane:EtOAc (8:1 to 4:1 gradient) as the eluent to obtain 8.0 g (90%) of the product as colorless crystalline solid. Analysis of this 25 substance (Mp 95-96° C. MS (FAB) m/z 237 (MH)⁺; ¹H NMR (CDCl₃) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.23 (s, 6H), 1.40-1.58 (m, 3H), 4.65 (s, 2H), 6.17 (m, 1H), 6.38 (m, 2H)) revealed it to be 4-(1,1,5-trimethylhexyl) resorcinol:



EXAMPLE 5

This example demonstrates the synthesis of a compound according to Formula I.

A solution of 4-(1,1,5-trimethylhexyl) resorcinol from Example 4 (2 g, 0.0076 mole) in anhydrous CH_2Cl_2 (10 mL) was cooled in ice-bath and was treated dropwise with a solution of boron tribromide in CH_2Cl_2 (2.6 mL of 1M solution, 0.0026 mole).
 5 The mixture was stirred in the cold bath for 2 h and then at room temperature overnight. The mixture was cooled in ice-bath and cautiously treated with water (10 mL) followed by saturated aqueous sodium bicarbonate (5 mL). The organic layer was separated, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by chromatography over a column of silica using cyclohexane:EtOAc (8:1 to 4:1
 10 gradient) as the eluent to obtain 0.364 g (19%) of the product as a colorless oil. Analysis of this substance (MS (FAB) m/z 251 (MH^+); ^1H NMR (CDCl_3) δ 0.80 (d, 6H), 1.00-1.10 (m, 4H), 1.24 (s, 6H), 1.4-1.6 (m, 3H), 3.78 (s, 3H), 4.67 (s, 1H), 6.23 (m, 1H), 6.40 (m, 1H), 6.47 (m, 1H)) revealed it to be 3-methoxy-5-(1,1,5-trimethylhexyl)phenol:



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EXAMPLE 6

This example demonstrates the antiviral activity of several compounds according to the invention.

Compounds. Compounds indicated in Table 1 were prepared as varying concentrations in SDMSA and used fresh.
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Latently Infected Cells. 5×10^3 U1 cells (obtained from the AIDS Research and Reference Reagent Program, Bethesda, MD) were plated in 96-well plates with media with or without 5ng/ml TNF α and a test compound. After 3 to 6 days incubation, the supernatants and cells were assessed.

PBMC Isolation and Blasting. Peripheral blood mononuclear cells (PBMC) obtained from healthy HIV- and hepatitis-negative patients were washed to remove residual gradient separation material. The washed cells were then counted, and their viability assessed. Following this initial preparation, the cells are suspended in RPMI 1640 medium supplemented with 15 % inactivated fetal bovine serum, 2 nM L-glutamine, 100 U/ml penicillin, 100 $\mu\text{g}/\text{ml}$ streptomycin, and 10 $\mu\text{g}/\text{ml}$ gentamycin with 2 $\mu\text{g}/\text{ml}$ PHA at 1×10^6 cells/ml. Following a 2 to 3 day incubation (37°C , 5 % CO_2), the cells were collected by centrifugation, washed, and resuspended in the same
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medium, supplemented with recombinant IL-2. The cultures were then maintained until use by $\frac{1}{2}$ volume change with fresh IL-12 containing medium every 3 days.

PBMC Assay. When ready for use, PBMCs from a minimum of two donors that have been blasted with PHA and IL-1 were mixed, counted, and viability determined by trypan blue exclusion. The cells were then resuspended in 1×10^6 cells/ml in RPMI 5 1640 supplemented with 15% fetal bovine serum (heat inactivated), 2mM L-glutamine, 100 U/ml penicillin, 100 μ g/ml streptomycin, 10 μ g/ml gentamycin and IL-2 (20U/ml). 10 50 μ l of cells were then distributed to the inner 60 wells of a 96 well plate. Each plate contains cell control wells (cells only), virus control wells (cells plus virus), drug 15 toxicity control wells (cells plus test compound), drug colorimetric control wells (drug only) as well as experimental wells (drug plus cells plus virus). Diluted compounds were then added to the microliter plate followed by the appropriate pre-titered strain of HIV-1. All samples were assayed in triplicate with a sister plate for the determination of compound toxicity. The final volume per well was 200 μ l. The assay was incubated for 15 7 days at 37 °C, 5% CO₂, after which supernatants were collected for analysis of RT activity and sister plates for assessment of cell viability.

Monocyte Isolation and Culture. Peripheral blood monocytes (PBM) were obtained from healthy HIV- and hepatitis- negative donors by ficoll hypaque 20 purification (optionally using recombinant IFN γ). After 7 days, the cultures were washed to remove non adherent cells, and test compounds were added followed by HIV-1. Cultures were washed a final time by media removal 24 hours post infection, fresh test 25 compound was added, and the cultures continued for an additional seven days. Virus replication was then measured by expression of supernatant p24 antigen by commercially available ELISA assays. AZT was used as a positive control run in parallel with each determination.

XTT Staining for Viability. Absence of toxicity was assessed by reduction of 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]2H-tetrazolium 30 hydroxide (XTT). 50 μ l of a solution containing 1 mg/ml XTT and 0.06 μ g/ml phenazine methanesulfate (PMS) was added per well, and the plate was incubated for 4 hours at 37 °C. Adhesive plate sealers were used in place of the lids so that the sealed 35 plates could be inverted several times to mix the soluble reaction product. Following this incubation, the plates were read spectrophotometrically at 450 nm to assess the degree of reduction product.

Analysis of p24. Viral protein production (p24) was assessed by standard 35 ELISA.

Reverse Transcriptase Assay. HIV reverse transcriptase was measured in cell free supernatants. Titrated TTP was resuspended in distilled H₂O at 5 Ci/ml. Poly rA and oligo dT were prepared as a stock solution which was kept at -20 °C. The RT

reaction buffer (125 µl 1M EGTA, 125 µl dH₂O, 110 µl 10% SDS, 50 µl 1M Tris (pH 7.4), 50 µl 1M DTT, and 40 Ml 1M MgCl₂) was prepared fresh. The three solutions were then mixed together in a ratio of 2 parts TTP, 1 part polyrA:oligo dT, and 1 part buffer. Ten µl of this reaction mixture was then placed in a round bottom microliter plate, and 15 µl of virus-containing supernatant was added. The plate was incubated at 37 °C in a water bath with a solid support for 60 minutes. Following the reaction, the volume was spotted onto pieces of DE81 paper, washed 5 times for 5 minutes each in a 5% sodium phosphate buffer, 2 times for 1 minute in distilled water, 2 times for 1 minute each in 70% ethanol, and then dried. Opti-Fluor O was then added to each sample and incorporated radioactivity was quantified using a scintillation counter.

Data Analysis. IC₅₀ (i.e., 50% inhibition of virus replication), TC₅₀ (50% cytotoxicity), and a selectivity index (SI = IC₅₀/TC₅₀) were calculated for each assay. Pooled data for all compounds tested are presented in Table 1. The results indicate that 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid, cannabidiol, and olivitol, 5-(1,1,5-trimethylhexyl) resorcinol, and 5-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol exhibited moderate antiviral activity. The antiviral activity of olivitol was more pronounced in the PBMCs and TNFα induced U1 cells than in monocytes/macrophages or uninduced U1 cells. Particularly with reference to the cannabinoids, these results are surprising, given observations that some such compounds can enhance, rather than suppress HIV replication (see, e.g., Noe et al., Chapter 25 in *Drug of Abuse, Immunomodulation and AIDS*, Friedman et al., Ed., (Plenum Press, NY 1998)).

EXAMPLE 7

This example demonstrates the antineoplastic activity of compounds according to Formula 1.

Cell Lines. Cell lines indicated in table 2 were propagated under sterile conditions in RPMI 1640 or DMEM with 10 % fetal calf serum, 2 mM L-glutamine, and sodium bicarbonate ("complete medium") and incubated at 37 °C 5% CO₂ and 95 % humidity. Each cell line was subcultured once or twice weekly, and were periodically screened for mycoplasma contamination (positive cultures were cured over three passages with antibiotic). Only cultures free of mycoplasma were used for antineoplastic assessment.

Antineoplastic Assessment. Cells from each cell line were harvested, pelleted to remove the media, and then suspended in fresh complete medium. The cell count was determined and viability was measured with propidium iodide staining. The cells were adjusted with complete medium to a density of 5 x 10³ cells/ml. Tissue culture plates were seeded with 100 µl samples of each cell line, and the plates were incubated overnight to allow for cell anchorage and acclimation.

Following acclimation, the compounds indicated in table 2 were diluted in complete medium. A range of eight concentrations was used to treat the cell cultures. For each dilution, eight wells are each treated with 100 μ l of dosing solution. Each culture plate contains a cell control (8 wells, mock treated with complete medium), a medium control (7 wells with medium used to subtract out signal generated by media conditions), a solvent control (8 wells), and an air blank (1 well) for calibrating the plate reader. Each cell line was also treated with a single dose of doxorubicin (1 μ M, eight wells) as a positive control for cytotoxicity. Once dosing was completed, the cells were incubated at 37 °C in 5 % CO₂ and 95 % humidity.

Five days after treatment, the cells were analyzed for antineoplastic effects using the SRB assay to calculate IC₅₀ for each treatment. The results are presented in Table 2. The results indicate that 5-(26-dimethyl-2-heptyl)resorcinol exhibited an IC₅₀ of 77-95 μ M in six cell lines, indicating that such compounds have antineoplastic effects.

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INCORPORATION BY REFERENCE

All sources (e.g., inventor's certificates, patent applications, patents, printed publications, repository accessions or records, utility models, world-wide web pages, and the like) referred to or cited anywhere in this document or in any drawing, Sequence Listing, or Statement filed concurrently herewith are hereby incorporated into and made part of this specification by such reference thereto.

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GUIDE TO INTERPRETATION

The foregoing is an integrated description of the invention as a whole, not merely of any particular element or facet thereof. The description describes "preferred embodiments" of this invention, including the best mode known to the inventors for carrying it out. Of course, upon reading the foregoing description, variations of those preferred embodiments will become obvious to those of ordinary skill in the art. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

As used in the foregoing description and in the following claims, singular indicators (e.g., "a" or "one") include the plural, unless otherwise indicated. Recitation of a range of discontinuous values is intended to serve as a shorthand method of referring individually to each separate value falling within the range, and each separate value is incorporated into the specification as if it were individually listed. As regards the claims in particular, the term "consisting essentially of" indicates that unlisted

ingredients or steps that do not materially affect the basic and novel properties of the invention can be employed in addition to the specifically recited ingredients or steps. In contrast, the terms "comprising" or "having" indicate that any ingredients or steps can be present in addition to those recited. The term "consisting of" indicates that only the recited ingredients or steps are present, but does not foreclose the possibility that equivalents of the ingredients or steps can substitute for those specifically recited.

Table 1

Compound	Monocyte/macrophage assay with HIV-1(p24) IC_{50}				PBMC HIV-1 (RT) IC_{50}				TNF induced U1 cells (RT) IC_{50}			
	TC_{50}	TI	IC_{50}	TC_{50}	IC_{50}	TC_{50}	TI	IC_{50}	TC_{50}	TI	IC_{50}	TC_{50}
AZT (μM)	0.001 0.0061	>4 >4	>4000 655.7	0.00021 0.0056	>4 >4	>1904 714.2	---	---	---	---	---	---
DdC (μM)	0.0028	>10	>3,571	0.0876	>10	>101.0 1176	---	---	---	---	---	---
Cannabinol ($\mu g/ml$)	7.7	13.07	1.7	6.91	7.66	1.11	5.14	5.26	1.0	NA	NA	NA
Cannabidiol ($\mu g/ml$)	8.18	22.87	2.8	1.52	7.76	5.11	2.76	7.8	2.8	NA	NA	NA
11-nor- $\Delta 9$ -tetrahydrocannabidiol-9-carboxylic acid ($\mu g/ml$)	7.79	76.73	9.8	39.09	71.1	1.82	6.69	23.71	3.55	NA	NA	NA
$\Delta 8$ tetrahydrocannabinol ($\mu g/ml$)	>0.1	>0.1	NA	0.08	>0.1	>1.25	0.06	>0.1	>1.667	NA	NA	NA
$\Delta 9$ tetrahydrocannabinol ($\mu g/ml$)	>0.1	>0.1	NA	0.07	>0.1	1.43	0.06	0.088	1.47	NA	NA	NA
EtOH (%)	0.06	>.1	>1.67	>0.1	>0.1	NA	>0.1	>0.1	>0.1	NA	NA	NA
Olivitol (μM)	63.7	75.9	1.19	16.9	>100	5.9	22.5	77.5	3.45	NA	NA	NA
Resorciol (μM)	NA	NA	NA	>200	>200	---	NA	NA	NA	NA	NA	NA
Orcinol (μM)	NA	NA	NA	>200	>200	---	NA	NA	NA	NA	NA	NA
5-(1,1,5-trimethylhexyl) resorciol (μM)	NA	NA	NA	14.8	44.6	3	NA	NA	NA	NA	NA	NA
5-(1,1,5-trimethylhexyl)-2,6-dimethoxyphenol (μM)	NA	NA	NA	15.8	50.9	3.2	NA	NA	NA	NA	NA	NA
5-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene (μM)	NA	NA	NA	>200	>200	---	NA	NA	NA	NA	NA	NA
3-methoxy-5-(1,1,5-trimethylhexyl)phenol (μM)	NA	NA	NA	39.9	46.4	1.2	NA	NA	NA	NA	NA	NA

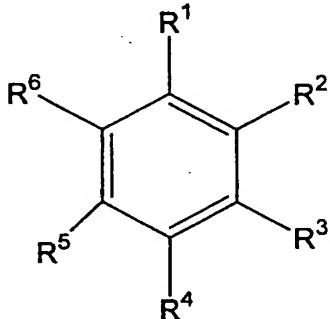
Table 2
IC₅₀ Values in µg/ml (IC₅₀ Molar Values)

Compound	SNB-7 (CNS)	DLD-1 (colon)	NCI-H23 (lung)	ZR-75-1 (mammary)	LOX IMVI (melanoma)	PC-3 (prostate)	CAKI-1 (renal)
5-(2,6-dimethyl-2-heptyl)resorcinol	2.2x10 ¹ (9.5x10 ⁻⁵)	2.1x10 ¹ (9.0x10 ⁻⁵)	1.8x10 ¹ (7.7x10 ⁻⁵)	1.9x10 ¹ (8.1x10 ⁻⁵)	NA	2.0x10 ¹ (8.4x10 ⁻⁵)	2.2x10 ¹ (9.3x10 ⁻⁵)
olivetol	4.0x10 ¹ (2.2x10 ⁻⁴)	4.2x10 ¹ (2.3x10 ⁻⁴)	3.3x10 ¹ (1.8x10 ⁻⁴)	3.6x10 ¹ (2.0x10 ⁻⁴)	4.4x10 ¹ (2.4x10 ⁻⁴)	3.7x10 ¹ (2.0x10 ⁻⁴)	4.0x10 ¹ (2.2x10 ⁻⁴)

WHAT IS CLAIMED IS:

1. A method of treating a disease or disorder associated with an immune dysfunction, comprising administering to a patient having a disease or disorder associated with immune dysfunction a pharmacologically-acceptable composition comprising at least one compound selected from the group of compounds consisting of 5-alkyl-resorcinols, cannabinoids, cannabidiols, cannabigerols, and combinations thereof.

5 2. The method of claim 1, wherein at least one compound is a 5-alkyl-resorcinol derivative having the following formula:



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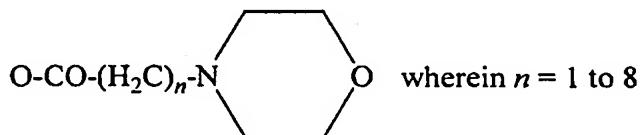
wherein,

R¹ is:

- a) H,
- b) a C₁₋₄ alkyl group or ester thereof,
- c) COOH,
- d) OH,
- e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di-methylamino or ethylamino groups,
- f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
- g)

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- h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative; or
- i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded,

comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R² is: a) H, OH, or a halogen
 b) C₁₋₆ carboxy or alkoxy group, or
 c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
 ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
 c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

R⁴ is: a) H,
 b) OH,
 c) C₁₋₆ alkoxy or carboxyl

R⁵ is: H or OH; and

R⁶ is: a) H or OH;
 b) C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof,

- c) O-C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof, or
- d) a pryeny, gerenyl, or farnesyl group, optionally substituted at any position with one or more halogens,
- e) (W)_m-Y-(Z)_n, wherein

5 W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

10 Z is:
i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

15 m and n are the same or different, and each is either 0 or 1,

20 f) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

25 g) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different.

3. The method of claim 2, wherein R¹ is OH or OCH₃.

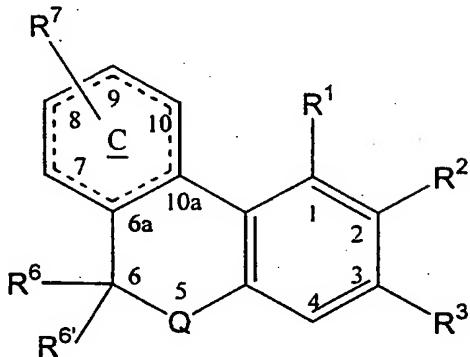
4. The method of claim 2, wherein R² is H or OH.

30 5. The method of claim 2, wherein R³ is a branched C₆₋₁₂ alkyl group containing at least one double bond.

6. The method of claim 5, wherein R³ is 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl.

7. The method of claim 2, wherein R⁶ is methyl or ethyl.

8. The method of claim 1, wherein at least one compound is cannabinol or a derivative thereof having the following formula:

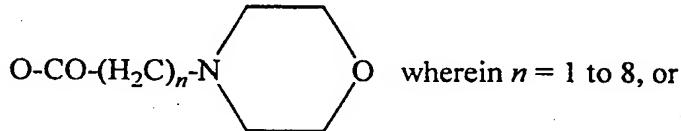


wherein,

R¹ is:

- 5 a) H,
- b) a C₁₋₄ alkyl group or ester thereof,
- c) COOH,
- d) OH,
- e) a methoxy or O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,

10 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
g)



15 h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

20 i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

25 R² is:

- a) H, OH or a halogen
- b) C₁₋₆ carboxy or alkoxy group, or
- c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded,

comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,

5 optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkene, alkyne, or haloalkyl, optionally substituted with a terminal aromatic ring,

10 ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

15 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can

be the same or different, and wherein

m and n are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

20 c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

25 R⁶ and R^{6'} together form =O or =S, or each is independently selected from the group consisting of:

a) hydrogen,

30 b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,

c) CN,

d) CO₂H,

e) CO₂-C₁₋₄ alkyl,

f) C(Y)(Z)-OH,

35 g) C(Y)(Z)-O-C₁₋₄ alkyl, and

h) C₁₋₆ alkyl-CO₂-Y,

wherein Y and Z are each independently H or C₁₋₆ alkyl,

R⁷ is: a) hydroxy or lactone,

b) halo.

c) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,

d) CN,

e) N₃,

f) CO₂H,

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g) CO₂-C₁₋₄ alkyl,

h) C(Y)(Z)-OH,

i) C(Y)(Z)-O-C₁₋₄ alkyl,

j) C₁₋₆ alkyl-CO₂-Y, or

k) =O or =S,

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wherein Y and Z are each independently H or C₁₋₆ alkyl;

Q is: a) O or S, or

b) N-W, wherein W is:

i) hydrogen,

ii) C₁₋₆ alkoxyalkyl, C₁₋₆ alkyl, or C₁₋₆ haloalkyl

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iii) OC₁₋₆ alkyl, or OC₁₋₆ haloalkyl,

iv) CN,

v) C₁₋₆ alkyl,

vi) C(Y)(Z)C₁₋₄ alkyl, or

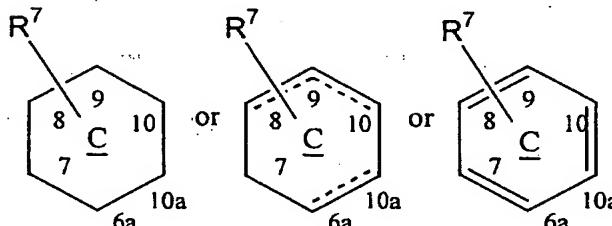
vii) C₁₋₆ alkyl-CO₂-Z,

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wherein Y and Z are each independently H or C₁₋₆ alkyl; and

C is:

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, wherein the dashed lines represent a double bond at either the Δ6, Δ8, or Δ9

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position.

9. The method of claim 8, wherein R¹ and R² form an O,2 propano ring.

10. The method of claim 8, wherein R¹ is H or OH.

11. The method of claim 8, wherein R¹ is methoxy.

12. The method of claim 8, wherein R² is iodo.

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13. The method of claim 8, wherein R³ is dimethylheptyl (DMH), dimethylpentyl (DMP), or have halogenated or bulky terminal groups.

14. The method of claim 13, wherein R³ is 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl.

15. The method of claim 8, wherein R³ is -(CH₂)₁₋₆-CON(CH₃)₂.

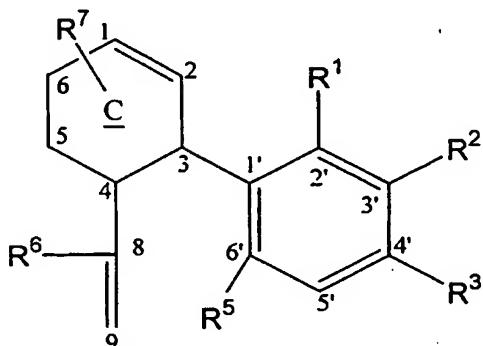
16. The method of claim 8, wherein R³ comprises a haloalkyl group.

17. The method of claim 8, wherein R⁶ and R^{6'} together form =O or each are methyl, ethyl, or methoxy.

5 18. The method of claim 8, wherein R⁷ is at position 9 of said C ring.

19. The method of claim 8, wherein R⁷ is COOH, halogen, β-hydroxy, or lactone.

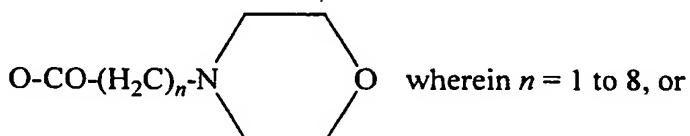
20. The method of claim 1, wherein at least one compound is cannabidiol or a derivative thereof having the following formula:



10 wherein:

R¹ is: a) H,
 b) a C₁₋₄ alkyl group or ester thereof
 c) COOH,
 d) OH,
 e) a methoxy or O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di- methylamino or ethylamino groups,
 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,

15 g)



20

25 h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

5 R² is: a) H, OH, or a halogen
 b) C₁₋₆ carboxy or alkoxy group, or
 c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

10 R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

15 Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
 ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyltio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

20 m and n are the same or different, and each is either 0 or 1,
 b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different,

25 c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

30 35 R⁵ is a) H
 b) a C₁₋₄ alkyl group
 c) COOH
 d) OH, or

e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group;

R⁶ is:

- a) hydrogen,
- b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,
- c) CN,
- d) CO₂H,
- e) CO₂-C₁₋₄ alkyl,
- f) C(Y)(Z)-OH,
- g) C(Y)(Z)-O-C₁₋₄ alkyl, or
- h) C₁₋₆ alkyl-CO₂-Y,

wherein Y and Z are each independently H or C₁₋₆ alkyl,

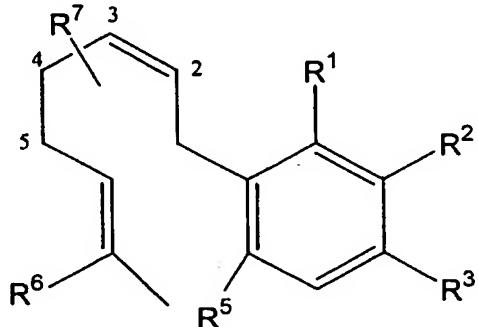
R⁷ is: a) hydroxy or lactone,

- b) halo,
- c) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, C₁₋₆ carboxy, or C₁₋₆ haloalkyl,
- d) CN,
- e) N₃,
- f) CO₂H,
- g) CO₂-C₁₋₄ alkyl,

- h) C(Y)(Z)-OH,
- i) C(Y)(Z)-O-C₁₋₄ alkyl,
- j) C₁₋₆ alkyl-CO₂-Y, or
- k) =O or =S,

wherein Y and Z are each independently H or C₁₋₆ alkyl, and wherein R⁷ can be at any of positions 1, 2, 5, or 6 of ring C.

21. The method of claim 1, wherein at least one compound is cannabigerol or a derivative thereof having the following formula:

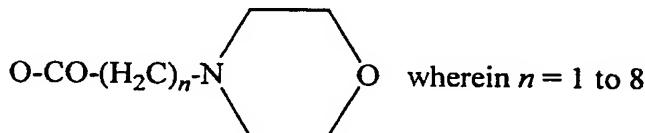


wherein:

R¹ is: a) H,

5 b) a C₁₋₄ alkyl group or ester thereof
 c) COOH,
 d) OH,
 e) a methoxy or O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono-
 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,

10 g)



20 h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative; or
 i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

25 R² is: a) H, OH or a halogen

b) C₁₋₆ carboxy or alkoxy group, or

c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

30 R³ is: a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyltio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

m and *n* are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different.

10

c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

15

R^5 is a) H
b) a C_{1-4} alkyl group
c) COOH
d) OH, or
e) a $O-C_{1-5}$ alkyl or alkanoyl, optionally substituted with at least one mono- or di- methylamino or ethylamino group;

20

R^6 is:

- a) hydrogen,
- b) C_{1-6} alkoxy , C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
- c) CN,
- d) CO_2H ,
- e) CO_2-C_{1-4} alkyl,
- f) $C(Y)(Z)-OH$,
- g) $C(Y)(Z)-O-C_{1-4}$ alkyl, or
- h) C_{1-6} alkyl- CO_2-Y ,

wherein Y and Z are each independently H or C_{1-6} alkyl,

30

R^7 is: a) hydroxy or lactone.

35

R^7 is:

- a) hydroxy or lactone,
- b) halo,
- c) C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, or C_{1-6} haloalkyl,
- d) CN,
- e) N_3 ,
- f) CO_2H ,
- g) CO_2-C_{1-4} alkyl,
- h) $C(Y)(Z)-OH$,

i) C(Y)(Z)-O-C₁₋₄ alkyl,

j) C₁₋₆ alkyl-CO₂-Y, or

k) =O or =S,

wherein Y and Z are each independently H or C₁₋₆ alkyl, and wherein R⁷ can be at any of positions 2-5.

5 22. The method of claim 1, wherein the composition includes at least two of the compounds.

23 The method of claim 1, wherein the composition is adjunctively delivered in conjunction with at least one antiviral agent.

10 24. The method of claim 23, wherein an antiviral agent is selected from the group of agents consisting of abacavir, azidothymidine cidofovir, delavirdine mesylate, didanosine, dideoxycytidine, efavirenz, foscarnet, ganciclovir, indinavir sulfate, lamivudine, nelfinavir mesylate, nevirapine, ritonavir, saquinavir, saquinavir mesylate, stavudine, and zalcitabine.

15 25. The method of claim 1, wherein the patient is a mammal selected from the group of animals consisting of monkeys, cats, dogs, horses, cows, pigs, goats, and sheep.

26. The method of claim 1, wherein the patient is human.

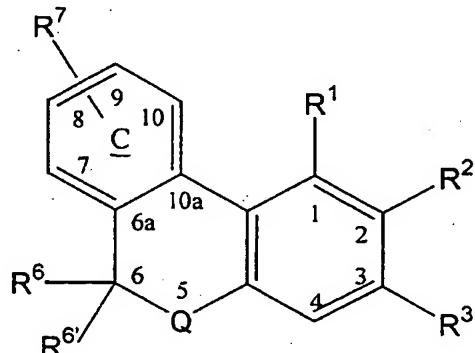
27. The method of claim 26, wherein said disease or disorder is HIV disease.

20 28. The method of claim 27, wherein the method attenuates the reduction of CD4⁺ cells within said patient.

29. The method of claim 27, wherein the method increases the number of CD4⁺ cells within said patient.

25 30. The method of claim 27, wherein the method decreases the viral load within said patient.

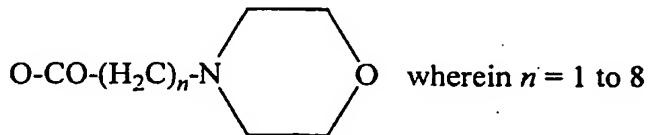
31. A cannabinol derivative that attenuates replication of HIV and that has following formula:



wherein

R¹ is: a) H,

b) a C₁₋₄ alkyl group or ester thereof
 c) COOH,
 d) OH,
 e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di-methylamino or ethylamino groups,
 f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
 g)



15 h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;
 i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

20 R² is: a) H, OH, or a halogen
 b) C₁₋₆ carboxy or alkoxy group, or
 c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

25 R³ is: a) (W)_m-Y-(Z)_n, wherein

30 W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, or N(C₁₋₆ alkyl),

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof,

optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different. or

iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

5

m and *n* are the same or different, and each is either 0 or 1,

10

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different,

10

c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

15

R⁶ and R^{6'} together form =O or =S, or each is independently selected from the group consisting of:

20

- a) hydrogen,
- b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,
- c) CN,
- d) CO₂H,
- e) CO₂-C₁₋₄ alkyl,
- f) C(Y)(Z)-OH,
- g) C(Y)(Z)-O-C₁₋₄ alkyl, and
- h) C₁₋₆ alkyl-CO₂-Y,

25

wherein Y and Z are each independently H or C₁₋₆ alkyl,

30

R⁷ is:

- a) hydroxy or lactone,
- b) halo,
- c) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,
- d) CN,
- e) N₃,
- f) CO₂H,
- g) CO₂-C₁₋₄ alkyl,
- h) C(Y)(Z)-OH,
- i) C(Y)(Z)-O-C₁₋₄ alkyl,
- j) C₁₋₆ alkyl-CO₂-Y, or
- k) =O or =S,

35

wherein Y and Z are each independently H or C₁₋₆ alkyl;

Q is:

- a) O or S, or

b) N-W, wherein W is:

- i) hydrogen,
- ii) C₁₋₆ alkoxyalkyl, C₁₋₆ alkyl, or C₁₋₆ haloalkyl
- iii) OC₁₋₆ alkyl, or OC₁₋₆ haloalkyl
- iv) CN,
- v) C₁₋₆ alkyl,
- vi) C(Y)(Z)C₁₋₄ alkyl, or
- vii) C₁₋₆ alkyl-CO₂-Z,

wherein Y and Z are each independently H or C₁₋₆ alkyl.

5 32. The cannabinol derivative of claim 31, wherein R¹ is H, an ester, or an ether.

10 33. The cannabinol derivative of claim 31, wherein R² is iodo.

15 34. The cannabinol derivative of claim 31, wherein R³ is a branched alkyl, alkene, or alkyne chain.

15 35. The cannabinol derivative of claim 31, wherein R³ is dimethylheptyl (DMH), dimethylpentyl (DMP), or has halogenated or bulky terminal groups.

20 36. The cannabinol derivative of claim 31, wherein R³ is 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl.

20 37. The cannabinol derivative of claim 31, wherein R³ is -(CH₂)₁₋₆-CON(CH₃)₂.

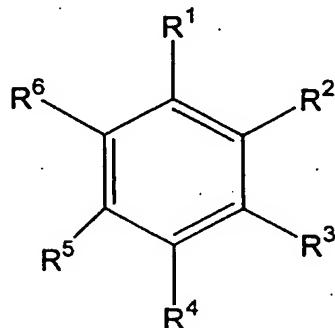
25 38. The cannabinol derivative of claim 31, wherein R³ is haloalkyl.

25 39. The cannabinol derivative of claim 31, wherein R⁶ and R^{6'} together form =O or are each ethyl.

25 40. The cannabinol derivative of claim 31, wherein R⁷ is at position 9 of said C ring.

25 41. The cannabinol derivative of claim 31, wherein R⁷ is COOH, halogen, β-hydroxy, or lactone.

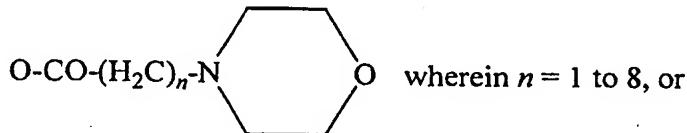
25 42. An alkylated resorcinol derivative that has following formula:



wherein,

R¹ is: a) H,

- b) a C₁₋₄ alkyl group or ester thereof,
- c) COOH,
- d) OH,
- e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or di-methylamino or ethylamino groups,
- f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,
- g)



15 h) a p-aminobenzyl group or a C1-7 aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

R² is: H, OH, or a halogen; or

20 R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅-, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

R³ is: a) (W)_m-Y-(Z)_n, wherein

25 W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,

30 ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

35 iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyltio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different.

wherein at least one of W and Z includes a branched chain and wherein m and n are the same or different, and each is either 0 or 1,

5 b) a terminally-branched C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

10 c) a terminally-branched C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

15 R⁴ is: a) H,
b) OH,
c) C₁₋₆ alkoxy or carboxyl

R⁵ is: H or OH; and

20 R⁶ is: a) H or OH;
b) C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof;
c) O-C₁₋₄ alkyl, alkenyl, alkynyl, group, or mixture thereof;
d) a pryenyl, gerenyl, or farnesyl group, optionally substituted with a halogen;
e) (W)_m-Y-(Z)_n, wherein

25 W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

30 Z is: i) a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen, optionally substituted with a terminal aromatic ring,
ii) CN₁₋₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyltio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different,

wherein at least one of W and Z includes a branched chain and wherein m and n are the same or different, and each is either 0 or 1,

5 f) a terminally-branched C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
10 g) a terminally-branched C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different

43. The alkylated resorcinol derivative of claim 42, wherein R¹ is OH or OCH₃.

44. The alkylated resorcinol derivative of claim 42, wherein R² is H.

15 45. The alkylated resorcinol derivative of claim 42, wherein R³ is a terminally-branched C₆₋₁₂ alkyl group containing at least one double bond.

46. The alkylated resorcinol derivative of claim 45, wherein R³ is 1,1,5-trimethylhexyl, 1,1,5,5-tetramethylhexyl, or 1,1,5-trimethyl-hept-4-enyl.

20 47. The alkylated resorcinol derivative of claim 42, wherein R³ includes a chain of carbon atoms having at least one double bond at a carbon atom between C₄ and C₁₀ of the chain.

48. The alkylated resorcinol derivative of claim 42, wherein R³ includes a chain of carbon atoms having an odd number of carbon atoms.

25 49. The alkylated resorcinol derivative of claim 42, wherein R⁶ is methyl or ethyl.

50. A method of inhibiting the growth of a neoplasm, comprising delivering an alkylated resorcinol derivative of claim 42 to the neoplasm under conditions sufficient for the growth of the neoplasm to be inhibited.

30 51. The method of claim 50, wherein the alkylated resorcinol derivative is delivered to the neoplasm under conditions sufficient to potentiate apoptosis within cells of the neoplasm.

52. The method of claim 50, wherein the alkylated resorcinol derivative is adjunctively delivered in conjunction with the delivery of at least one other antineoplastic agent.

35 53. The method of claim 50, wherein the neoplasm is within a tumor, and the method attenuates the growth of the tumor.

54. The method of claim 50, wherein the neoplasm is within a blood dyscrasia, and the method attenuates the growth of the blood dyscrasia.

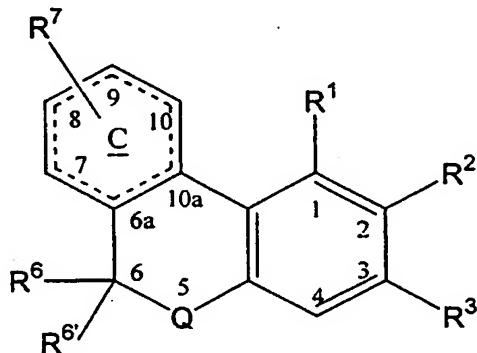
55. The method of claim 50, wherein the neoplasm is *in vivo*.

56. The method of claim 54, wherein the alkylated resorcinol derivative is delivered to the neoplasm by introducing it into systemic circulation.

57. The method of claim 55, wherein the alkylated resorcinol derivative is introduced into systemic circulation through the gastric, intestinal, oral, or rectal wall or via intravenous injection.

58. The method of claim 50, wherein the alkylated resorcinol derivative is delivered to the neoplasm by intratumoral injection.

59. A cannabinol or a derivative thereof having the following formula:



10 wherein,

R¹ is: a) H,

b) a C₁₋₄ alkyl group or ester thereof,

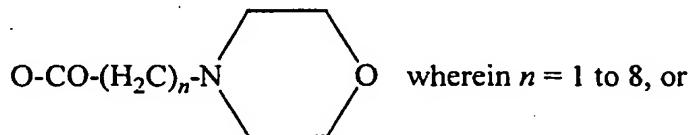
c) COOH,

d) OH,

15 e) a O-C₁₋₅ alkyl or alkanoyl, optionally substituted by mono- or dimethylamino or ethylamino groups,

f) a O-CO-C₃₋₁₀ alkyl group containing a carboxyl or amino group,

g)



20

h) a p-aminobenzyl group or a C₁₋₇ aminoalkyl group or an organic or mineral acid addition salt thereof, an isocyanate or isothiocyanate

25 derivative of the p-aminobenzyl or aminoalkyl group, a carboxyl terminated derivative of the aminoalkyl group having from 1 to 7 additional carbon atoms or a salt thereof, and an activated derivative of the carboxyl terminated derivative;

i) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

5 R² is:

- a) H, OH or a halogen
- b) C₁₋₆ carboxy or alkoxy group, or
- c) R¹ and R² comprise a substituent of the formula -O(CH₂)₃₋₅, wherein R¹ and R², together with the carbon atoms to which they are bonded, comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen.

10 R³ is: a terminally branched chain having the following formula:

a) (W)_m-Y-(Z)_n, wherein

W is a C₅₋₁₂ alkyl, alkenyl, alkynyl, group, or mixture thereof, optionally substituted with at least one halogen,

15 Y is a bond, O, S, SO, SO₂, CO, NH, N(C₁₋₆ alkyl), or NCS,

Z is:

- i) a C₅₋₁₂ alkyl, alkene, alkyne, or haloalkyl, optionally substituted with a terminal aromatic ring,
- ii) CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or
- iii) a phenyl or benzyl group, optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, CN, CF₃, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, and wherein

20

m and n are the same or different, and each is either 0 or 1,

b) a C₅₋₁₂ alkyl or haloalkyl group, optionally substituted with a terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different, or

25

c) a C₅₋₁₂ alkene or alkyne group, optionally substituted with a halogen, ditholene, terminal aromatic ring, CN₁₋₃, NCS, CO₂H, or CO₂C₁₋₄ alkyl, CONH₂, CONHC₁₋₄ alkyl, or CON(C₁₋₄ alkyl)₂, wherein each C₁₋₄ alkyl on the amide nitrogen can be the same or different;

30

35 R⁶ and R^{6'} together form =O or =S, or each is independently selected from the group consisting of:

- a) hydrogen,
- b) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,

c) CN,
d) CO₂H,
e) CO₂-C₁₋₄ alkyl,
f) C(Y)(Z)-OH,
g) C(Y)(Z)-O-C₁₋₄ alkyl, and
h) C₁₋₆ alkyl-CO₂-Y,

wherein Y and Z are each independently H or C₁₋₆ alkyl;

R⁷ is: a) hydroxy or lactone,

b) halo,
c) C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, or C₁₋₆ haloalkyl,
d) CN,
e) N₃,
f) CO₂H,
g) CO₂-C₁₋₄ alkyl,

h) C(Y)(Z)-OH,
i) C(Y)(Z)-O-C₁₋₄ alkyl,
j) C₁₋₆ alkyl-CO₂-Y, or
k) =O or =S,

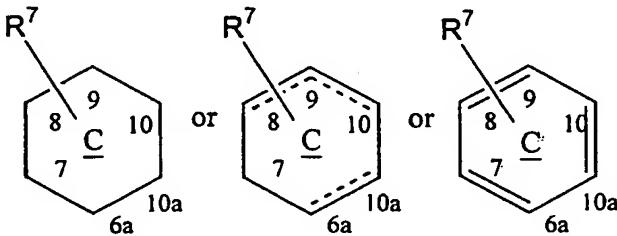
wherein Y and Z are each independently H or C₁₋₆ alkyl;

Q is: a) O or S, or

b) N-W, wherein W is:
i) hydrogen,
ii) C₁₋₆ alkoxyalkyl, C₁₋₆ alkyl, or C₁₋₆ haloalkyl
iii) OC₁₋₆ alkyl, or OC₁₋₆ haloalkyl,
iv) CN,
v) C₁₋₆ alkyl,
vi) C(Y)(Z)C₁₋₄ alkyl, or
vii) C₁₋₆ alkyl-CO₂-Z,

wherein Y and Z are each independently H or C₁₋₆ alkyl; and

C is:



35

, wherein the dashed lines represent a double bond at either the Δ6, Δ8, or Δ9 position.

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): IMMUGEN PHARMACEUTICALS, INC. [US/US]; 7400 S.W. Red Road, PMB 2, Suite 4, Miami, FL 33143 (US).

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 00/56303 A3

(54) Title: TREATMENT OF IMMUNE DISEASES

(57) Abstract: The present invention provides a method, compounds, and compositions for treating a disease associated with immune dysfunction. In accordance with the method, a pharmacologically-acceptable composition including at least one compound selected from the group of compounds consisting of 5-alkyl-resorcinol derivatives, cannabinol derivatives, cannabidiol derivatives, cannabigerol derivatives, and combinations thereof is administered to a patient under conditions sufficient to attenuate the dysfunction within the immune system. The invention also provides an antiviral cannabinol derivative that can be used in the inventive method. The invention also provides an alkylated resorcinol derivative and a method of using the alkylated resorcinol derivative to attenuate the growth of a neoplasm. The method and compound are useful for treating diseases of the immune system, such as HIV disease and neoplastic disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/05 A61K31/09 A61K31/661 A61P31/18 A61P35/00
A61K31/352

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, CHEM ABS Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LYMAN WD ET AL: "Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis" JOURNAL OF NEUROIMMUNOLOGY, XX, ELSEVIER SCIENCE PUBLISHERS BV, vol. 23, no. 1, 1989, pages 73-81, XP002114259 ISSN: 0165-5728 abstract ----- -/-	1,8-19, 22,23, 25,26, 31-41,59

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 February 2001

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARRIS L S ET AL: "ANTI TUMOR PROPERTIES OF CANNABINOIDES" 1976 , BRAUDE, MONIQUE C AND STEPHEN SZARA (ED) PHARMACOLOGY OF MARIHUANA,, PAGE(S) 749-762 , PROCEEDINGS OF THE MEETING SAVANNAH, GA, USA, DEC 3-6, 1974 XVII+458P(VOL 1); XVIII+404P(VOL 2) ILLUS RAVEN PRESS: NEW YORK, N Y, USA ISBN 0-89004-067-2 1976 XP000957683 page 749; figures 1-9; tables 1-3 page 752, paragraph 5 -page 760, paragraph 1 ---	1
X	HARRIS L S ET AL: "STRUCTURE ANTI TUMOR ACTIVITY OF CANNABINOIDES" PHARMACOLOGIST, vol. 17, no. 2, 1975, page 265 XP000957659 ISSN: 0031-7004 abstract	1-4, 42-44, 48,50-58
X	BAEK SEUNG HWA ET AL: "Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells." ARCHIVES OF PHARMACAL RESEARCH (SEOUL), vol. 21, no. 3, June 1998 (1998-06), pages 353-356, XP000957635 ISSN: 0253-6269 abstract; figure 3; tables 1,2 page 354, column 2, paragraph 6 -page 356, column 1, paragraph 1	1-4, 42-44, 48,50-58
X	SRIVASTAVA M D ET AL: "DELTA 9 TETRAHYDROCANNABINOL AND CANNABIDIOL ALTER CYTOKINE PRODUCTION BY HUMAN IMMUNE CELLS" IMMUNOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV,XX, vol. 40, no. 3, October 1998 (1998-10), pages 179-185, XP000957596 ISSN: 0162-3109 abstract page 183, column 1, paragraph 2 page 184, column 1, paragraphs 3,4	1,8-20, 22-41,59
X	NAHAS, GABRIEL ET AL: "Inhibitor effect of 5-amylresorcinol on lymphoblastic transformation" C. R. HEBD. SEANCES ACAD. SCI., SER. D (1974), 279(19), 1607-8, 1974, XP000957652 the whole document	1-4, 42-44, 48,50-58

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BHARGAVA H.N.: "Potential therapeutic applications of naturally occurring and synthetic cannabinoids" GENERAL PHARMACOLOGY, vol. 9, no. 4, 1978, pages 195-213, XP000981417 the whole document	1-21, 31-59
E	DATABASE WPI Section Ch, Week 200050 Derwent Publications Ltd., London, GB; Class B05, AN 2000-545825 XP002151974 & JP 2000 191520 A (SAKUMA K), 11 July 2000 (2000-07-11) abstract	1-5, 22, 23, 25-30, 42-45
X	NICHOLS D E ET AL: "ALLYL BENZENE ANALOGS OF DELTA-9 TETRA HYDRO CANNABINOL AS TUMOR GROWTH INHIBITORS" LIFE SCIENCES, vol. 21, no. 9, 1977, pages 1245-1248, XP000957664 EN ISSN: 0024-3205 the whole document	1-4, 42-44, 48, 50-58
X	HARTMANN, ROLF W. ET AL: "Antiestrogens. Synthesis and evaluation of mammary tumor inhibiting activity of 1,1,2,2-tetraalkyl-1,2-diphenylethananes" J. MED. CHEM., vol. 23, no. 8, 1980, pages 841-848, XP000953148 the whole document	1-5, 42-45, 47, 48, 50-58
X	CARCHMAN, R. A. ET AL.: "Cannabinoids and neoplastic growth" MARIHUANA: CHEM., BIOCHEM., CELL. EFF., PROC. SATELL. SYMP. (1976), 1975, pages 329-345, XP000981329 the whole document	50-53, 55-58
X	BURSTEIN S. ET AL.: "Further studies on the inhibition of Leydig cell testosterone production by cannabinoids" BIOCHEMICAL PHARMACOLOGY, vol. 29, no. 14, 1980, pages 2153-2154, XP000979796 the whole document	50-53, 55-58

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAEK, SEUNG-HWA ET AL.: "Synthesis and antitumor activity of cannabigerol" ARCH. PHARMACAL RES., vol. 19, no. 3, 1996, pages 228-230, XP000979791 the whole document ---	42-53, 55-58
X	WO 97 11668 A (MECHOULAM RAPHAEL ;YISSUM RES DEV CO (IL); GALLILY RUTH (IL); SHOH) 3 April 1997 (1997-04-03) abstract page 3, line 25 -page 5, line 16 page 6, line 4 -page 10, line 5 page 11, line 8 -page 13, line 15; claims 1-19; examples 7,8 ---	1,8-19, 22,23, 25,26, 31-41,59
X	GALLILY, R., ET AL.: "Protection against septic shock and suppression of tumor necrosis factor .alpha. and nitric oxide production by dexanabinol (HU-211), a nonpsychotropic cannabinoid" J. PHARMACOL. EXP. THER., vol. 283, no. 2, 1997, pages 918-924, XP000981331 abstract page 918, column 1; figures 4,5 ---	1,8-19, 22,23, 25,26, 31-41,59
X	ZHENG, Z.M. ET AL.: "Inhibition by .DELTA.-9-tetrahydrocannabinol of tumor necrosis factor-.alpha. production by mouse and human macrophages" INT. J. IMMUNOPHARMACOL., vol. 14, no. 8, 1992, pages 1445-1452, XP000979762 abstract; figure 12; tables 1,2 ---	1,8-19, 22,23, 25,26, 31-41,59
X	ELKIN R ET AL: ".DELTA.-9 TETRAHYDROCANNABINOL A NOVEL TREATMENT FOR INFLAMMATORY DEMYELINATION" FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY. ANNUAL MEETING. ABSTRACTS OF PAPERS, 29 April 1987 (1987-04-29), XP002114261 abstract ---	1,8-19, 22,23, 25,26, 31-41,59
X	SPECTER S ET AL: "MARIJUANA AND IMMUNOSUPPRESSION IN MAN" WATSON, R. R. (ED.). DRUGS OF ABUSE AND IMMUNE FUNCTION. IX+237P. CRC, 1990, pages 73-86, XP000979809 1990 page 76, paragraph 3 -page 79, paragraph 1; tables 1-5 ---	1,8-19, 22,23, 25,26, 31-41,59

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Creation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WATZL, B. ET AL.: "Influence of marijuana components (THC and CBD) on human mononuclear cell cytokine secretion in vitro" ADV. EXP. MED. BIOL., vol. 288, 1991, pages 63-70, XP000979761 page 63, paragraph 1 page 67; table 1 page 68, paragraph 2 -page 69, paragraph 2	1,8-20, 22-41,59
X	ZURIER ROBERT B ET AL: "Dimethylheptyl-THC-11 OIC acid: A nonpsychoactive antiinflammatory agent with a cannabinoid template structure." ARTHRITIS & RHEUMATISM, vol. 41, no. 1, January 1998 (1998-01), pages 163-170, XP000957594 ISSN: 0004-3591 the whole document	1,8-19, 22,23, 25,26, 31-41,59
X	TIMPONE J. G. ET AL.: "The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome" AIDS RES. HUM. RETROVIRUSES, vol. 13, no. 4, 1997, pages 305-315, XP000979121 abstract	1,8-19, 22-41,59

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SPECTER S ET AL: "SUPPRESSION OF IMMUNITY BY FRIEND LEUKEMIA VIRUS AND DELTA-9 TETRAHYDROCANNABINOL" FASEB (FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY), vol. 4, no. 4, 1990, page A1021 XP000979172 1990 ISSN: 0892-6638 abstract	1,8-19, 22-41,59
X	CABRAL, G. A.; VASQUEZ, R.: "Marijuana decreases macrophage antiviral and antitumor activities" ADV. BIOSCI. (OXFORD), vol. 80, 1991, pages 93-105, XP000981421 abstract	1,8-12, 22-26, 28-41,59
X,P	WO 99 52524 A (FELDMANN MARC ;MALFAIT ANNE MARIE (GB); MATHILDA & TERENCE KENNEDY) 21 October 1999 (1999-10-21) abstract page 4, line 1 -page 6, line 14; claims 1-12; figures 1-11; examples 1-9; tables 1-7	1-22,25, 26, 28-49,59
X,P	WO 99 53917 A (GRIMALDI MAURIZIO ;US HEALTH (US); AXELROD JULIUS (US); HAMPSON AI) 28 October 1999 (1999-10-28) abstract page 3, line 20 -page 8, line 4 page 11, line 12-27; example 10 page 25-29; claims 1-25	1-49,59
X	WAKSMAN YAAKOV: "Cannabidiol supresses proinflammatory mediators release from rat microglial cells and hepatic Kupffer macrophages." JOURNAL OF AUTOIMMUNITY, no. SUPPL., 1999, page 56 XP000979878 2nd International Congress on Autoimmunity; Tel Aviv, Israel; March 7-11, 1999 ISSN: 0896-8411 abstract	1,20,25, 26

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	SINGH, SHEO B. ET AL.: "Chemistry and biology of cylindrolols: novel inhibitors of Ras farnesyl-protein transferase from <i>Cylindrocarpus lucidum</i> " J. ORG. CHEM., vol. 61, no. 22, 1996, pages 7727-7727, XP000979162 abstract page 7727, column 1 -page 7723, column 1, paragraph 3 ---	50-53, 55-58
X	BEUTLER, J. A.: "Cytotoxic Geranyl Stilbenes from <i>Macaranga schweinfurthii</i> " J. NAT. PROD., vol. 61, no. 12, 1998, pages 1509-1512, XP000979832 the whole document ---	50-53, 55-58
A	WO 97 40006 A (MARRIOTT JONATHAN ; JARMAN MICHAEL (GB); NEIDLE STEPHEN (GB); CANCE) 30 October 1997 (1997-10-30) the whole document ---	1-59

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/07629

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-30,50-58 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-59 relate to an extremely large number of possible compounds/therapeutic applications. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole scope of the claims impossible.

Consequently, the search for the first invention has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the synthetic examples 1-5 and the compounds for which pharmacological data were provided, namely the compounds specifically mentioned in tables 1-2 per se and in relation to the following therapeutic applications (as specifically claimed): anti-HIV activity and anti-neoplastic activity.

No support in the description can be found for 5-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene of table 1: In accordance with example 3 of the description, this was considered to be an obvious error and searched as 4-(1,1,5-trimethylhexyl)-2,6-dimethoxybenzene (sic : this compound should be named 5-(1,1,5-trimethylhexyl)-1,3-dimethoxybenzene).

Claim 6 is not always dependent from claim 5.

Claims 2,8, 20, 21 31,42, 59 contain within the definition of R2 the expression: "comprises a ring where at least one hydrogen atom thereof is optionally substituted with a halogen". Hydrogen being monovalent, this expression is futile.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,22-30 (partially), 2-7,42-58

An alkylated resorcinol derivative of the formulae as specified in claims 1,2-7,42-58, as far as not comprised in invention 3 or 4 and use of this compound for the manufacture of a medicament for treating a disease or disorder associated with an immune dysfunction including HIV disease and for inhibiting the growth of a neoplasm.

2. Claims: 1,22-30 (partially), 8-19,31-41,59

A cannabinol of the formulae as specified in claims 8-19,31-41,59, and use of this compound in the manufacture of a medicament for treating a disease or disorder associated with an immune dysfunction including HIV disease.

3. Claims: 1,22-30 (partially), 20

Use of a cannabidiol of the formulae as specified in claim 20 in the manufacture of a medicament for treating a disease or disorder associated with an immune dysfunction including HIV disease.

4. Claims: 1,22-30 (partially), 21

Use of a cannabigerol of the formulae as specified in claim 21 in the manufacture of a medicament for treating a disease or disorder associated with an immune dysfunction including HIV disease.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/07629

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